# Novel Compounds

The present invention relates to certain novel pyrimidone and pyridone compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of atherosclerosis.

WO 95/00649 (SmithKline Beecham plc) describes the phospholipase $A_2$ enzyme Lipoprotein Associated Phospholipase $A_2$ (Lp-$PLA_2$), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, Arterioscler Thromb Vas Biol 1996:16;591-9) wherein it is referred to as LDL-$PLA_2$. A later patent application (WO 95/09921, Icos Corporation) and a related publication in Nature (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-$PLA_2$ and suggest that it may have potential as a therapeutic protein for regulating pathological inflammatory events.

It has been shown that Lp-$PLA_2$ is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-$PLA_2$ action are biologically active with lysophosphatidylcholine, in particular having several pro-atherogenic activities ascribed to it including monocyte chemotaxis and induction of endothelial dysfunction, both of which facilitate monocyte-derived macrophage accumulation within the artery wall. Inhibition of the Lp-$PLA_2$ enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

A recently published study (WOSCOPS – Packard et al, *N. Engl. J. Med.* 343 (2000) 1148-1155) has shown that the level of the enzyme Lp-$PLA_2$ is an independent risk factor in coronary artery disease.

The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-$PLA_2$ could therefore prove beneficial in the treatment of this phenomenon. An Lp-$PLA_2$ inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

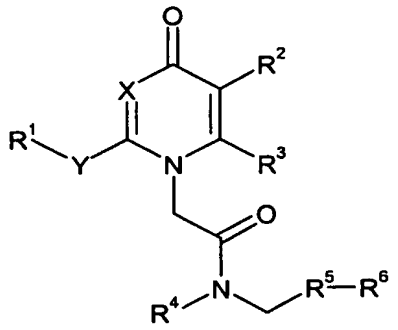
In addition, Lp-$PLA_2$ inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-$PLA_2$. Examples of such disorders include psoriasis.

Furthermore, Lp-$PLA_2$ inhibitors may also have a general application in any disorder that involves lipid oxidation in conjunction with Lp-$PLA_2$ activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, ischaemia, reperfusion injury and acute and chronic inflammation.

Patent applications WO 96/12963, WO 96/13484, WO 96/19451, WO 97/02242, WO 97/217675, WO 97/217676, WO 96/41098, and WO 97/41099 (SmithKline Beecham plc) disclose *inter alia* various series of 4-thionyl/sulfinyl/sulfonyl azetidinone compounds which are inhibitors of the enzyme Lp-$PLA_2$. These are irreversible, acylating inhibitors (Tew *et al*, Biochemistry, **37**, 10087, 1998).

A further class of compounds has now been identified which are non-acylating inhibitors of the enzyme Lp-$PLA_2$. Thus, WO 99/24420, WO 00/10980, WO 00/66566, WO 00/66567, WO 00/68208 and PCT/EP01/11562 (unpublished at the priority date of the present application) (SmithKline Beecham plc) disclose classes of pyrimidone compounds. PCT/EP01/11610 (SmithKline Beecham plc), also unpublished at the priority date of the instant application, discloses a class of pyridone compounds. We have now found that the amide nitrogen substituent on both the pyrimidone and pyridone ring scaffolds may be replaced, to give compounds having good activity as inhibitors of the enzyme Lp-$PLA_2$.

Accordingly, the present invention provides a compound of formula (I):



(I)

in which:

$R^1$ is an aryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, $C_{(1-6)}$alkylthio, aryl$C_{(1-6)}$alkoxy, hydroxy, halogen, CN, $COR^7$, carboxy, $COOR^7$, $NR^7COR^8$, $CONR^9R^{10}$, $SO_2NR^9R^{10}$, $NR^7SO_2R^8$, $NR^9R^{10}$, mono to perfluoro-$C_{(1-4)}$alkyl, mono to perfluoro-$C_{(1-4)}$alkoxyaryl, and aryl$C_{(1-4)}$alkyl;

$R^2$ is halogen, $C_{(1-3)}$alkyl, $C_{(1-3)}$alkoxy, hydroxy$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylthio, $C_{(1-3)}$alkylsulphinyl, amino$C_{(1-3)}$alkyl, mono- or di-$C_{(1-3)}$alkylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylcarbonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkoxy$C_{(1-3)}$alkylcarbonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylsulphonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylcarboxy, $C_{(1-3)}$alkylcarboxy$C_{(1-3)}$alkyl, and

$R^3$ is hydrogen, halogen, $C_{(1-3)}$alkyl, or hydroxy$C_{(1-3)}$alkyl; or

$R^2$ and $R^3$ together with the pyridone or pyrimidone ring carbon atoms to which they are attached form a fused 5-or 6-membered carbocyclic ring; or

$R^2$ and $R^3$ together with the pyridone or pyrimidone ring carbon atoms to which they are attached form a fused benzo or heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from halogen, $C_{(1-4)}$alkyl, cyano, $C_{(1-3)}$alkoxy$C_{(1-3)}$alkyl, $C_{(1-4)}$alkoxy or $C_{(1-4)}$alkylthio, or mono to perfluoro-$C_{(1-4)}$alkyl;

$R^4$ is $(CH_2)_n$ substituted by a substituent selected from benzimidazole or a 5- or 6-membered heteroaryl, each of which may optionally be substituted by one or more $R^{11}$;

$R^5$ is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, $C_{(1-6)}$alkylthio, aryl$C_{(1-6)}$alkoxy, hydroxy, halogen, CN, $COR^7$,

carboxy, $COOR^7$, $NR^7COR^8$, $CONR^9R^{10}$, $SO_2NR^9R^{10}$, $NR^7SO_2R^8$, $NR^9R^{10}$, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy;

$R^6$ is an aryl or a heteroaryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy, $C_{(1-6)}$alkylthio, $C_{(1-6)}$alkylsulfonyl, aryl$C_{(1-6)}$alkoxy, hydroxy, halogen, CN, $COR^7$, carboxy, $COOR^7$, $CONR^9R^{10}$, $NR^7COR^8$, $SO_2NR^9R^{10}$, $NR^7SO_2R^8$, $NR^9R^{10}$, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy, or $C_{(5-10)}$alkyl;

$R^7$ and $R^8$ are independently hydrogen or $C_{(1-12)}$alkyl, for instance $C_{(1-4)}$alkyl (e.g. methyl or ethyl);

$R^9$ and $R^{10}$ which may be the same or different is each selected from hydrogen, or $C_{(1-12)}$alkyl, or $R^9$ and $R^{10}$ together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from hydroxy, oxo, $C_{(1-4)}$alkyl, $C_{(1-4)}$alkylcarboxy, aryl, e.g. phenyl, or aralkyl, e.g benzyl, for instance morpholine or piperazine;

$R^{11}$ is selected from the group consisting of halogen, $CF_3$, $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy $C_{(1-6)}$alkyl or benzyl optionally substituted by $CF_3$, $C_{(1-6)}$alkyl, $C_{(1-6)}$alkoxy or halogen;

X is CH or nitrogen;

Y is $C_{(2-4)}$alkylene group (optionally substituted by 1, 2 or 3 substituents selected from methyl and ethyl), CH=CH, or $(CH_2)_mS$;

n is 1, 2, 3 or 4; and

m is 1 or 2.

In another aspect the invention provides a compound of formula (I) as defined above in which $R^1$ is an aryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from halogen, $C_{(1-6)}$alkyl, trifluoromethyl or $C_{(1-6)}$alkoxy.

Representative examples of $R^1$ when an aryl group include phenyl. Preferably, $R^1$ is phenyl optionally substituted by 1, 2, 3 or 4 halogen substituents, preferably, from 1 to 3 fluoro, more preferably, 2,3-difluoro or 4-fluoro.

In another aspect the present invention provides a compound of formula (I) as defined above in which, when X is CH, $R^2$ and $R^3$ together with the pyridone

ring carbon atoms to which they are attached form a fused benzo or pyrido ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from halogen, $C_{(1-4)}$alkyl, cyano, $C_{(1-3)}$alkoxy$C_{(1-3)}$alkyl, $C_{(1-4)}$alkoxy or $C_{(1-4)}$alkylthio, or mono to perfluoro-$C_{(1-4)}$alkyl.

Representative examples of $R^2$ and $R^3$ include when $R^2$ and $R^3$, together with the pyridone ring carbon atoms to which they are attached, form an unsubstituted fused benzo or pyrido ring.

In another aspect the present invention provides a compound of formula (I) as defined above in which, when X is nitrogen, $R^2$ and $R^3$ together with the pyrimidone ring carbon atoms to which they are attached form a fused 5-membered carbocyclic (cyclopentenyl) or benzo ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from halogen, $C_{(1-4)}$alkyl, cyano, $C_{(1-3)}$alkoxy$C_{(1-3)}$alkyl, $C_{(1-4)}$alkoxy or $C_{(1-4)}$alkylthio, or mono to perfluoro-$C_{(1-4)}$alkyl.

Representative examples of $R^2$ and $R^3$ include when $R^2$ and $R^3$, together with the pyrimidone ring carbon atoms to which they are attached, form an unsubstituted fused benzo or cyclopentenyl ring.

In another aspect the present invention provides a compound of formula (I) as defined above in which $R^4$ is $(CH_2)_n$ wherein n is 1 to 4 such as 1 to 3 substituted by benzimidazolyl, imidazolyl, thiazolyl, pyrazolyl, tetrazolyl and pyridyl, each of which may be optionally further substituted by one or more $R^{11}$. Preferred compounds are those in which the benzimidazolyl, imidazolyl, thiazolyl, pyrazolyl, tetrazolyl or pyridyl ring is unsubstituted or substituted by one or two substituents selected from halogen e.g. choro, fluoro and bromo, $C_{(1-6)}$ alkyl e.g $C_{(1-4)}$ alkyl, and $C_{(1-6)}$ alkoxy $C_{(1-6)}$ alkyl e.g $C_{(1-3)}$ alkoxy $C_{(1-3)}$ alkyl.

Representative examples of $R^4$ include methyl substituted by 1-methylimidazol-2-yl, pyrid-2-yl, 1-methylimidazol-4-yl, 1-ethylimidazol-4-yl, 1-isopropylimidazol-4-yl , 1-(2-methoxyethyl)imidazol-4-yl and tetrazol-5-yl.

Representative examples of $R^4$ include ethyl substituted at the 2-position by 1-methylimidazol-4-yl, 2-methylimidazol-1-yl, benzimidazol-2-yl, 5-chlorobenzimidazol-2-yl, imidazol-2-yl, imidazol-1-yl, 1-methylimidazol-5-yl, thiazol-2-yl, pyrazol-1-yl, tetrazol-5-yl, pyrid-2-yl, imidazol-4-yl, 1-ethylimidazol-4-yl, 1-isopropylimidazol-4-yl and 1-(2-methoxyethyl)imidazol-4-

yl, 4,5-dichloroimidazol-1-yl, 4,5-dichloro-2-methylimidazol-1-yl, 2-t-butylimidazol-l-yl, 4-chloro-2-methylimidazol-l-yl, 4-bromoimidazol-l-yl, 4-methylimidazol-l-yl, and 4-chloroimidazol-l-yl.

Representative examples of $R^4$ include propyl substituted at the 3-position by imidazol-1-yl, 1-methylimidazol-2-yl, 2-methylimidazol-1-yl, 1-methylimidazol-4-yl, pyrid-2-yl , 1-methylimidazol-5-yl, 1-ethylimidazol-4-yl, 1-iso-propylimidazol-4-yl, and 1-(2-methoxyethyl)imidzaol-4-yl.

Preferably $R^4$ is ethyl substituted at the 2-position by 1-methylimidazol-4-yl

In another aspect the present invention provides a compound of formula (I) as defined above in which $R^5$ is phenyl or pyridyl.

Representative examples of $R^5$ include phenyl.

In another aspect the present invention provides a compound of formula (I) as defined above in which $R^6$ is phenyl substituted by mono to perfluoro-$C_{(1-4)}$alkyl, halogen or $C_{(1-6)}$alkyl, in particular phenyl substituted by mono to perfluoro-$C_{(1-4)}$ alkyl.

Representative examples of $R^6$ include phenyl substituted by trifluoromethyl at the 4-position.

Preferably, $R^5$ and $R^6$ together form a 4-(phenyl)phenyl or a 2-(phenyl)pyridinyl substituent in which the remote phenyl ring may be optionally substituted by trifluoromethyl, preferably at the 4-position.

Representative examples of $R^{11}$ include methyl, ethyl, isopropyl, *t* butyl, chloro, bromo and methoxyethyl.

In another aspect, the present invention provides a compound of formula (I) as defined above in which Y is a $C_{(2-4)}$alkylene group or $CH_2S$.

Representative examples of Y when X is CH or nitrogen include $CH_2S$ and $(CH_2)_2$.

It is to be understood that the invention covers all combinations of particular aspects of the invention as described hereinabove.

It will be appreciated that compounds of the present invention may comprise one or more chiral centres so that stereoisomers may be formed. The present invention encompasses all stereoisomers of the compounds of formula (I) including geometric isomers and optical isomers(eg. diastereoisomers and enantiomers) whether as individual stereoisomers isolated such as to be substantially free of the other stereoisomers (ie. pure) or as mixtures thereof including racemic modifications. An individual stereoisomer isolated such as to be substantially free of other stereoisomer (ie. pure) will preferably be isolated such that less than 10% preferably less than 1% especially less than 0.1% of the other stereoisomers is present.

Certain compounds of formula (I) may exist in one of several tautomeric forms. It will be understood that the present invention encompasses all tautomers of the compounds of formula (I) whether as individual tautomers or as mixtures thereof.

It will be appreciated that in some instances, compounds of the present invention may include a basic function such as an amino group as a substituent. Such basic functions may be used to form acid addition salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, taurocholic acid, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, **66**, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

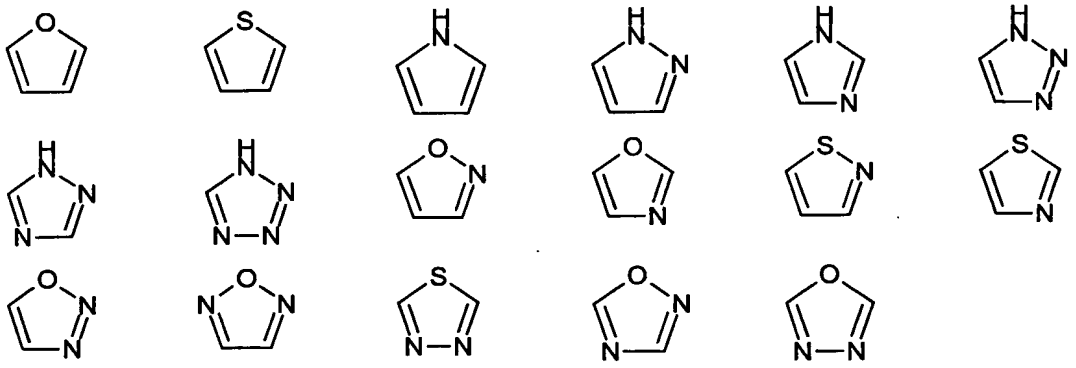
When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the term "aryl" refers to, unless otherwise defined, a mono- or bicyclic aromatic ring system containing up to 10 carbon atoms in the ring system, for instance phenyl or naphthyl.

When used herein, the term "heteroaryl" refers to a mono- or bicyclic heteroaromatic ring system comprising up to four, preferably 1 or 2, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring.

When used herein, the terms "halogen" and "halo" include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

When used herein the term "5-membered heteroaryl" means a heteroaryl selected from the following:



The term "6- membered heteroaryl" means a heteroaryl selected from the following:

Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I)

may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are re-crystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or re-crystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

Compounds of the present invention are inhibitors of the enzyme lipoprotein associated phospholipase $A_2$ (Lp-$PLA_2$) and as such are expected to be of use in therapy, in particular in the treatment of atherosclerosis. In a further aspect therefore the present invention provides a compound of formula (I) for use in therapy.

The compounds of formula (I) are inhibitors of lysophosphatidylcholine production by Lp-$PLA_2$ and may therefore also have a general application in any disorder that involves endothelial dysfunction, for example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of formula (I) may have a general application in any disorder that involves lipid oxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, ischaemia, reperfusion injury, sepsis, and acute and chronic inflammation.

Further applications include any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-$PLA_2$. Examples of such disorders include psoriasis.

Accordingly, in a further aspect, the present invention provides for a method of treating a disease state associated with activity of the enzyme Lp-$PLA_2$ which method involves treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme. The disease state may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidised free fatty acids; with lipid oxidation in conjunction with Lp-$PLA_2$ activity; or with endothelial dysfunction.

Compounds of the present invention may also be of use in treating the above mentioned disease states in combination with an anti-hyperlipidaemic, anti-atherosclerotic, anti-diabetic, anti-anginal, anti-inflammatory, or anti-hypertension agent or an agent for lowering Lp(a). Examples of the above include cholesterol synthesis inhibitors such as statins, anti-oxidants such as probucol, insulin sensitisers, calcium channel antagonists, and anti-inflammatory drugs such as NSAIDs. Examples of agents for lowering Lp(a) include the aminophosphonates described in WO 97/02037, WO 98/28310, WO 98/28311 and WO 98/28312 (Symphar SA and SmithKline Beecham).

A preferred combination therapy will be the use of a compound of the present invention and a statin. The statins are a well known class of cholesterol lowering agents and include atorvastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, lovastatin and rosuvastatin (also referred to as S-4522 or ZD 4522, Astra Zeneca). The two agents may be administered at substantially the same time or at different times, according to the discretion of the physician.

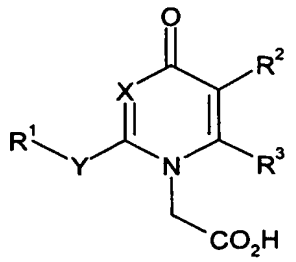
A further preferred combination therapy will be the use of a compound of the present invention and an anti-diabetic agent or an insulin sensitiser, as coronary heart disease is a major cause of death for diabetics. Within this class, preferred compounds for use with a compound of the present invention include the PPARgamma activators, for instance GI262570 (GlaxoSmithKline) and the glitazone class of compounds such as rosiglitazone (Avandia, GlaxoSmithKline), troglitazone and pioglitazone.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier, optionally with one or more other therapeutic compounds such as for example a statin or anti diabetic.

Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository. Compounds of formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule. Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration. A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule. Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I). The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

A compound of formula (I) may be prepared by reacting an acid compound of formula (II):



(II)

in which X, Y, $R^1$, $R^2$ and $R^3$ are as hereinbefore defined,
with an amine compound of formula (III):

$$R^6\text{-}R^5\text{-}CH_2NHR^4$$

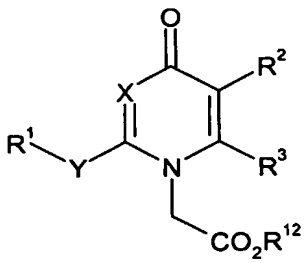
(III)

in which $R^4$, $R^5$ and $R^6$ are as hereinbefore defined; under amide forming conditions.

Suitable amide forming conditions are well known in the art and include treating the acid of formula (II) with the amine of formula (III) in the presence of a coupling agent such as 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (DEC) and 1-hydroxybenzotriazole (HOBt), or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and di-isopropylethylamine, in an aprotic solvent such as dichloromethane or dimethylformamide.

It will be appreciated by those skilled in the art that amines of formula (III) are either known compounds or may be prepared by literature methods such as reductive amination between suitable carbonyl and amine precursors, employing an appropriate reducing agent such as sodium triacetoxyborohydride or sodium borohydride. Such methods are described in "Comprehensive Organic Transformations: a guide to functional group preparations" by Richard Larock (VCH, 1989) , incorporated herein by reference.

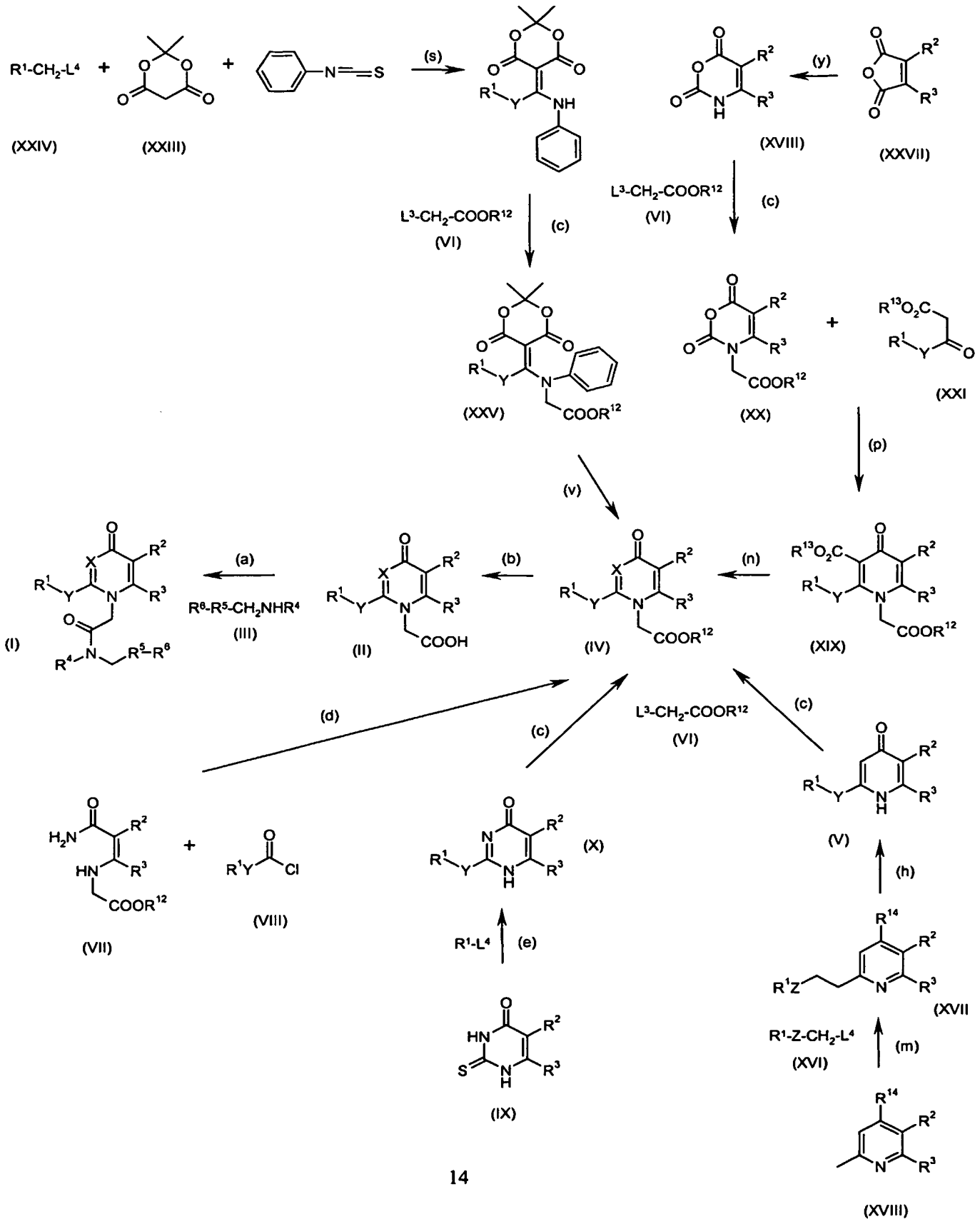
A compound of formula (II) may be readily prepared from a corresponding ester of formula (IV):



(IV)

in which X, Y, $R^1$, $R^2$ and $R^3$ are as hereinbefore defined, and $R^{12}$ is benzyl or $C_{(1-6)}$alkyl, for example ethyl or t-butyl, by treating with a de-esterifying agent, for instance, when $R^{12}$ is t-butyl, trifluoroacetic acid or when $R^{12}$ is ethyl or benzyl, sodium hydroxide in dioxan.

The overall synthesis of compounds of formula (I) is illustrated in the following scheme wherein $R^1$ to
$R^{12}$ are as hereinbefore defined:


(XXIV)
(XXIII)
(s)
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(y)
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(VI)
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(XX)
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(a)
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(II)
(b)
(IV)
(n)
(XIX)
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(VII)
(VIII)
(X)
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(IX)
(XVII)
(m)
(XVI)
(XVIII)

Referring to the scheme when X is CH, the ester (IV) may be prepared by N-1 alkylation of (V) using (VI), in which $L^3$ is a leaving group (e.g. Br) and $R^{12}$ is as hereinbefore defined e.g. (VI) is t-butyl bromoacetate or ethyl bromoacetate, in the presence of a base e.g. BuLi in THF, sodium hydride in N-methyl pyrrolidinone (NMP), or a secondary or teriary amine such as di-isopropylethylamine, in an inert solvent such as dichloromethane (step c).

Alternatively, when X is CH, Y is $CH_2S$, and $R^2$ and $R^3$, together with the pyridone ring carbon atoms to which they are attached, form a fused benzo ring, intermediate (IV) may be synthesised from known starting materials by steps (s), (c) and (v) in which:
(s) treatment of Meldrum's acid (XXIII) with sodium hydride at low temperature, followed by reaction with phenylisothiocyanate and subsequent treatment with $R^1CH_2$-$L^4$, where $L^4$ is a leaving group;
(c) as hereinbefore discussed;
(v) as hereinbefore discussed.

When X is CH and Y is alkylene, it is preferable to use steps (m), (h) and (c) (intermediates (XVIII), (XVII) and (V)) or steps (n) and (p) (intermediates (XIX), (XX), (XXI)) in which:
(m) chain extension of a 2-alkyl pyridine, e.g. where Y = $ZCH_2CH_2$ by treatment of a 2-methylpyridine (XVIII) with $R^1$-Z-$CH_2$-$L^4$ (XVI) in which $L^4$ is a leaving group and a strong base, such as BuLi, in THF.
(h) transformation of a 4-substituted pyridine into a 4-pyridone e.g. by treatment of (XVII) $R^{14}$ = Cl with aq HCl and dioxan, or deprotection of $R^{14}$ = Oallyl, e.g. using $(Ph_3P)_3RhCl$ when in aq. ethanol.
(c) as hereinbefore described.

In the alternative route, the 3-ester group is removed from intermediate (XIX) $R^{13}$ = $C_{(1-6)}$alkyl by heating in diphenyl ether where $R^{13}$ = tBu (step n);
Intermediate (XIX) is formed from the 2,6-dioxo-1,3-oxazine (XX) and ester (XXI) by treatment with a base such as NaH in DMF or 1,8-diazabicyclo[5.4.0]undec-7-ene in dichloromethane (step p).

Synthesis of (XX) from known starting materials may be achieved via steps (y) and (c) in which:

(y) treatment of (XXVII) with azidotrimethylsilane in tetrahydrofuran or dichloromethane;
(c) as hereinbefore described.

When X is nitrogen and Y is $CH_2S$ it is preferable to use steps (e) and (c) (intermediates (IX), (X)) in which:
(e) thioether forming reaction. Treatment of (IX) with $R^1$-$L^4$ in the presence of a base such as sodium ethoxide or potassium carbonate, preferably in a solvent such as ethanol, dimethyl formamide, or acetone, or a secondary or tertiary amine base such as di-isopropylethylamine, in a solvent such as dichloromethane.
(c) as hereinbefore described.

When X is nitrogen and Y is $(CH_2)_2$ it is preferable to react intermediate (VII) with intermediate (VIII) (step (d)) under standard pyrimidone ring forming conditions, in a solvent such as benzene.

It will be appreciated by those skilled in the art that all other starting materials and intermediates are either known compounds or may be prepared by literature methods, such as those described in "Comprehensive Organic Transformations: a guide to functional group preparations" by Richard Larock (VCH, 1989), incorporated herein by reference.

It will be appreciated that compounds of formula (I) may also be prepared from other compounds of formula (I) using conventional interconversion procedures. Thus, a process for preparing a compound of formula (I) by interconversion of another compound of formula (I) constitutes a further aspect of the present invention.

It will be appreciated by those skilled in the art that it may be desirable to use protected derivatives of intermediates used in the preparation of compounds of formula (I). Thus, the above processes may require deprotection as an intermediate or final step to yield the desired compound. Thus, according to another process, a compound of formula (I) may be prepared by subjecting a protected derivative of a compound of formula (I) to reaction to remove the protecting group or groups present, constituting a further aspect of the present invention.

Protection and deprotection of functional groups may be effected using conventional means. Thus, hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in Protective

Groups in Organic Chenistry, Ed, J F.W. McOmie (Plenum Press, 1973) or Protective Groups in Organic Synthesis by Theodora W. Green (John Wiley and Sons, 1991).

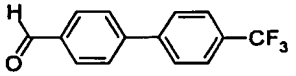
Examples of suitable hydroxyl protecting groups includes groups selected from alkyl (e.g. t-butyl or methoxymethyl), aralkyl (e.g. benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl (e.g. acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g. t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g. by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may be similarly be removed by solvolysis, e.g. by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved by hydrogenolysis in the presence of a Noble metal catalyst such as palladium-on-charcoal.

The present invention will now be illustrated by the following examples.

**Examples**

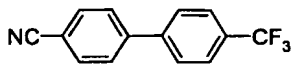
The structure and purity of the intermediates and examples was confirmed by 1H-NMR and (in nearly all cases) mass spectroscopy, even where not explicitly indicated below

**Intermediate A1 4-(4-Trifluoromethylphenyl)benzaldehyde**



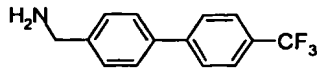
A 3 L 3-neck flask fitted with top stirrer, condenser and argon inlet/outlet was charged with 4-trifluoromethylbenzene boronic acid (90.0 g, 0.474 mol), 4-bromobenzaldehyde (83.29 g, 0.450 mol) and 1,2-dimethoxyethane (1.3 L), followed by 2M aqueous sodium carbonate (474 mL) and palladium acetate (5.32 g, 0.0237 mol). The stirring mixture was heated to reflux for 4 h under argon, then allowed to cool to room temperature over 16 h. The reaction mixture was filtered through hyflo. The filtrate was diluted with saturated brine and extracted 3x with ethyl acetate. The combined extracts were dried over magnesium sulfate and filtered through hyflo, giving a clear orange filtrate which was evaporated to a solid (ca. 120g, crude). Flash chromatography (silica, 10-50% dichloromethane in pet. ether, 10% steps) gave a white solid which dissolved in hexane (500mL) on boiling. Crystallisation, finally in ice, gave the title compound as a solid which was filtered off, washed with ice cold hexane and dried, (86.33g, 77%). $^1$H-NMR ($CDCl_3$) δ 7.77-8.03 (8H, m), 10.09 (1H, s).

**Intermediate A2 — 4-(4-Trifluoromethylphenyl)benzonitrile**



Prepared by the method of intermediate A1 using 4-trifluoromethylbenzeneboronic acid and 4-bromobenzonitrile. $^1$H-NMR (DMSO) δ 7.99-7.94 (6H, m) 7.86 (2H, d); MS(APCI+) found (M+1)=248, $C_{14}H_8F_3N$ requires 247.

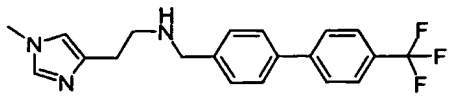
**Intermediate A3 — 4-(4-Trifluoromethylphenyl)benzylamine hydrochloride salt**



To a solution of intermediate A2 (96.7g, 0.39 mol) in absolute ethanol (5L) and concentrated hydrochloric acid (200 ml) was added 10% palladium on charcoal (30.0 g, 54% $H_2O$ paste). The mixture was stirred under 50psi hydrogen for 16h.

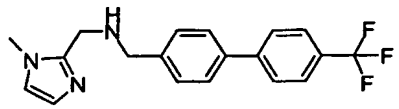
Additional 10% palladium on charcoal (25.0g, 54% $H_2O$ paste) was added and the mixture was stirred under 50psi hydrogen for a further 16h. The mixture was filtered through celite and the solvent evaporated to give the hydrochloride salt of the title compound as a cream solid (102.5g, 91%). $^1$H-NMR (DMSO) δ 8.61 (3H, s), 7.93 (2H, d), 7.83 (2H, d), 7.80 (2H, d), 7.65 (2H, d), 4.08 (2H, s); MS(APCI+) found (M-$NH_2$)=235, $C_{14}H_{12}F_3N$ requires 251.

**Intermediate A4 — *N* (2-(1-Methylimidazol-4-yl)ethyl)-4'-trifluoromethylbiphen-4-ylmethylamine**



To a solution of 2-(1-methylimidazol-4-yl)ethylamine dihydrochloride (1.59g) and diisopropylethylamine (2.45ml) in dry dimethylformamide (10ml) was added intermediate A1 (1.67g) in dry THF (80ml) followed by dried 4Å molecular sieves (12g). The mixture was stirred slowly for 0.5h and stood for 16h at room temperature. The solution was filtered and evaporated under reduced pressure to give a yellow oil that was dissolved in ethanol (50ml) and sodium borohydride (0.253g) was added portionwise under nitrogen. Vigourous gas evolution was observed. After 4.5h, the mixture was evaporated under reduced pressure, the residue treated with water, basified with 2M sodium hydroxide and extracted with dichloromethane. The extracts were washed with dilute brine, dried over sodium sulphate and evaporated under reduced pressure to a white solid. This solid was chromatographed on silica gel using 5-15% 2M ammonia in methanol:ethyl acetate to give the desired product (1.32g). $^1$H-NMR ($CDCl_3$) δ 2.79 (2H, t), 2.97 (2H, t), 3.62 (3H, s), 3.88 (2H, s), 6.66 (1H, s), 7.34 (1H, s), 7.43 (2H, d), 7.55 (2H, d), 7.68 (4H, br.s); LC/MS (ESI+) found (M+1) 360; $C_{20}H_{20}F_3N_3$ requires 359. LC/MS purity = 100%.

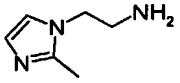
**Intermediate A5 — *N* (1-Methylimidazol-2-yl)methyl)-4'-trifluoromethylbiphen-4-ylmethylamine**



A mixture of 1-methylimidazol-2-ylcarboxaldehyde (0.5g), triethylamine (0.633ml), intermediate A3 (1.3g) and dried 4Å molecular sieves (12g) in dry dichloromethane (50ml) was stirred at room temperature under nitrogen for 4h. The solution was filtered and evaporated under reduced pressure to give a pink solid that was dissolved in ethanol (100ml) and sodium borohydride (0.258g) was added portionwise under nitrogen. Vigourous gas evolution was observed. The

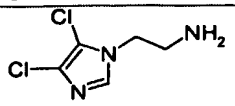
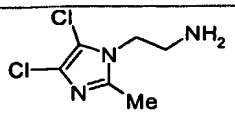
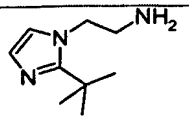
resulting mixture was stirred at room temperature overnight, the mixture was evaporated under reduced pressure, the residue treated with water and extracted with dichloromethane. The extracts were washed with brine, dried over sodium sulphate and evaporated under reduced pressure to a white solid. This solid was chromatographed on silica gel using ethyl acetate:cyclohexane, ethyl acetate, dichloromethane and methanol:dichloromethane as a gradient elution. This gave the desired product (1.09g). $^1$H-NMR ($CDCl_3$) δ 3.66 (3H, s), 3.88 (2H, s), 3.90 (2H, s), 6.84 (1H, d), 6.95 (1H, d), 7.45 (2H, d), 7.57 (2H, d), 7.68 (4H, br.s); LC/MS (ESI+) found (M+1) 346; $C_{19}H_{18}F_3N_3$ requires 345.

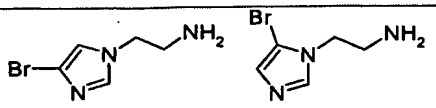
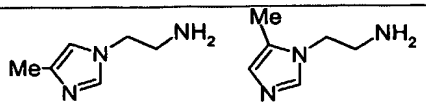
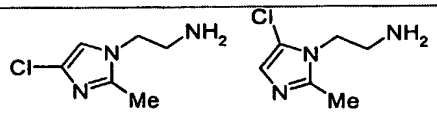
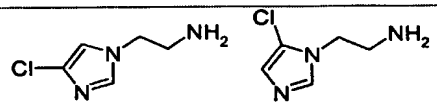
**Intermediate A6 - 2-(2-Methylimidazol-1-yl)ethylamine hydrobromide**



To finely ground sodium hydroxide (5.76g) in dry acetonitrile (20ml) was added 2-methylimidazole and the mixture stirred at room temperature (small exotherm observed). Tetrabutylammonium hydrogen sulphate (0.54g) and 2-chloroethylamine hydrochloride (4.99g) were added to the brown mixture. Further acetonitrile (20ml) was added and the mixture refluxed under nitrogen for 16h after which time a large amount of solid had precipitated. The mixture was cooled and the solid filtered off and washed with acetonitrile. The combined acetonitrile layers were evaporated under reduced pressure to an oil which was dissolved in ethanol (40ml) and 48% aq hydrobromic acid (5ml) added with stirring at 4°C. A white solid crystallised which was filtered, washed well with ethanol and dried. This gave the desired product (3.09g). $^1$H-NMR (DMSO) δ 2.31 (3H, s), 3.13 (2H, t), 4.08 (2H, t), 6.81 (1H, br.s), 7.12 (1H, br.s).

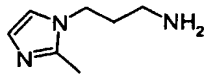
Similarly prepared by the method of Int A6 were

| Int. | Precursor | Structure | Name |
|---|---|---|---|
| A90 | A80 |  | 2-(4,5-Dichloroimidazol-1-yl)ethylamine hydrobromide |
| A91 | A81 |  | 2-(4,5-Dichloro-2-methylimidazol-1-yl)ethylamine hydrobromide |
| A92 | A86 |  | 2-(2-*t*-Butylimidazol-1-yl)ethylamine hydrobromide |

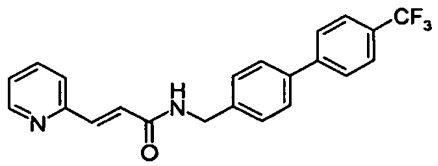
| | | | |
|---|---|---|---|
| A93 | A82 |  | Mixture of 2-(4-Bromoimidazol-1-yl)ethylamine hydrobromide and 2-(5-Bromoimidazol-1-yl)ethylamine hydrobromide |
| A94 | A83 |  | Mixture of 2-(4-Methylimidazol-1-yl)ethylamine hydrobromide and 2-(5-Methylimidazol-1-yl)ethylamine hydrobromide |
| A95 | A84 |  | Mixture of 2-(4-Chloro-2-methylimidazol-1-yl)ethylamine hydrobromide and 2-(5-Chloro-2-methylimidazol-1-yl)ethylamine hydrobromide |
| A96 | A85 |  | Mixture of 2-(4-Chloroimidazol-1-yl)ethylamine hydrobromide and 2-(5-Chloroimidazol-1-yl)ethylamine hydrobromide |

Similarly prepared with the method of intermediate A6 using 3-chloropropylamine hydrochloride was:

**Intermediate A7 - 3-(2-Methylimidazol-1-yl)propylamine hydrobromide**



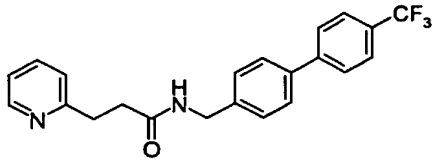
**Intermediate A8 – 3-(Pyrid-2-yl)-*N*-(4'-trifluoromethylbiphen-4-ylmethyl)prop-2-enoic acid amide**



To a mixture of intermediate A3 (0.193g) and 3-(pyrid-2-yl)prop-2-enoic acid (0.10g) in dry dimethylformamide (2.5ml) was added diisopropylethylamine (0.467ml) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.357g) with stirring at room temperature. The mixture was stirred for a further 2.5h and left overnight. The solvent was removed under reduced pressure and the residue partioned between dichloromethane and water. The aqueous layer was extracted with further

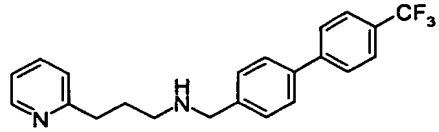
dichloromethane and the combined organic layers washed with 1M sodium hydroxide, water, brine and dried over sodium sulphate. Evaporation under reduced pressure gave a solid that was chromatographed on silica gel using cyclohexane:ethyl acetate to methanol:ethyl acetate as eluents. This gave the desired product (0.255g). $^1$H-NMR (DMSO) δ 4.48 (2H, d), 7.16 (1H, d), 7.34-7.40 (1H, m), 7.44 (2H, d), 7.52 (1H, d), 7.60 (1H, d), 7.73 (2H, d), 7.77-7.93 (5H, m), 8.62 (1H, d), 8.88 (1H, t); LC/MS (ESI+) found (M+1) 383; $C_{22}H_{17}F_3N_2O$ requires 382. LC/MS purity = 100%.

**Intermediate A9 - 3-(Pyrid-2-yl)-*N*-(4'-trifluoromethylbiphen-4-ylmethyl)propionamide**



A solution of intermediate A8 (0.251g) in ethanol (20ml) containing 10% palladium on charcoal (0.03g) was hydrogenated at room temperature and atmospheric pressure. After 5h, the solution was filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel using cyclohexane:ethyl acetate to methanol:ethyl acetate as eluents. This gave the desired product (0.225g). $^1$H-NMR ($CDCl_3$) δ 2.76 (2H, t), 3.17 (2H, t), 4.47 (2H, d), 6.80 (1H, br.m), 7.10-7.16 (1H, m), 7.22 (1H, d), 7.28 (2H, d), 7.52 (2H, d), 7.62 (1H, txd), 7.64-7.72 (4H, m), 8.46 (1H, d); LC/MS (ESI+) found (M+1) 385; $C_{22}H_{19}F_3N_2O$ requires 384. LC/MS purity = 100%.

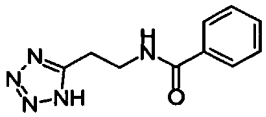
**Intermediate A10 – *N*-(3-(Pyrid-2-yl)propyl)-4'-trifluoromethylbiphen-4-ylmethylamine**



To a solution of intermediate A9 (0.5g) in dry tetrahydrofuran (15ml) under nitrogen, at room temprature, was added dropwise, 1M borane.THF complex (6.5ml). The resulting solution was stirred at room temperature for 0.5h and then at reflux for 2h. After cooling, the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with further ethyl acetate and the combined organics were washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The oil so formed was dissolved in THF

(5ml), 1M sodium hydroxide (1.5ml) added and the mixture heated to reflux for 48h. After cooling, the residue was partioned between dichloromethane (x2) and water and the combined organic layers were washed with further water and dried over sodium sulphate. Evaporation under reduced pressure gave a solid that was chromatographed on silica gel using cyclohexane:ethyl acetate, ethyl acetate, to methanol:dichloromethane as eluents. This gave the desired product (0.413g). $^1$H-NMR ($CDCl_3$) δ 1.98 (2H, m), 2.73 (2H, t), 2.87 (2H, t), 3.85 (2H, s), 7.07-7.18 (2H, m), 7.43 (2H, d), 7.50-7.65 (3H, m), 7.68 (4H, m), 8.52 (1H, d); LC/MS (ESI+) found (M+1) 371; $C_{22}H_{21}F_3N_2$ requires 370.

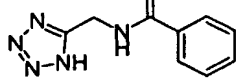
**Intermediate A11 – *N*-(2-(Tetrazol-5-yl)ethyl benzamide**



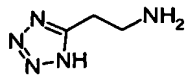
A mixture of N-(2-cyanoethyl)benzamide (6.97g), sodium azide (2.73g) and ammonium chloride (2.35g) was suspended in dry dimethylformamide (35ml) and the stirring mixture heated to 120°C (oil bath temperature 130°C) (Rocz. Chem. 1971, 45(6), 967-980). After 16h, the mixture was cooled and the solid residue triturated with 2M hydrochloric acid (80ml), filtered, washed well with water and dried. This gave the desired product (6.84g). $^1$H-NMR (DMSO) δ 3.16 (2H, t), 3.63 (2H, q), 7.43-7.57 (3H, m), 7.43 (2H, d), 7.77-7.83 (2H, m), 8.65 (1H, br.t); LC/MS (ESI+) found (M+1) 218; $C_{10}H_{11}N_5O$ requires 217. LC/MS purity = 100%.

Similarly prepared from N-cyanomethyl benzamide was:

**Intermediate A12 – *N*-(Tetrazol-5-ylmethyl)benzamide**



**Intermediate A13 – 2-(Tetrazol-5-yl)ethylamine hydrochloride**

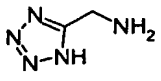


Intermediate A11 (6.0g) and concentrated aqueous hydrochloric acid (40ml) was reluxed for 24h. After cooling to 0°C for several hours, the precipitated solid was filtered off and the filtrate extracted with diethyl ether (x2). The aqueous layer was evaporated under reduced pressure to a white solid that was triturated with

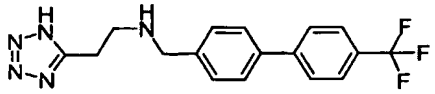
ethanol, filtered and dried. This gave the desired product (3.45g). $^1$H-NMR (DMSO) δ 3.1-3.6 (br.).

Similarly prepared from intermediate A12 was:

**Intermediate A14 – Tetrazol-5-ylmethylamine hydrochloride**

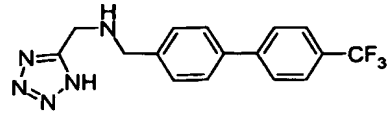


**Intermediate A15 — *N*-(2-(Tetrazol-5-yl)ethyl)-4'-trifluoromethylbiphen-4-ylmethylamine**



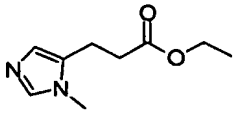
A mixture of intermediate A13 (1.0g) and diisopropylethylamine (1.22ml) in methanol (10ml) was stirred with warming, cooled and evaporated under reduced pressure. The residue was stirred in dry dichloromethane (50ml) and further diisopropylethylamine (1.22ml) was added. The mixture was evaporated under reduced pressure and dry dimethylformamide (10ml) followed by intermediate A1 (1.67g) and then tetrahydrofuran (80ml) followed by dried 4Å molecular sieves (10g). After 16h at room temperature, the mixture was filtered and evaporated under reduced pressure to give a yellow oil that was dissolved in ethanol (50ml) and sodium borohydride (0.253g) was added portionwise under nitrogen. Vigourous gas evolution was observed. After 16h, the mixture was evaporated under reduced pressure, the residue treated with water and acidified to pH6-7 with 2M hydrochloric acid. The white solid so formed was filtered off, stirred with methanol, filtered again and dried to give the desired product (1.54g). $^1$H-NMR (DMSO) δ 3.05 (2H, t), 3.15 (2H, t), 4.16 (2H, s), 7.59 (2H, d), 7.77-7.86 (4H, m), 7.93 (2H, d); LC/MS (ESI+) found (M+1) 348; $C_{17}H_{16}F_3N_5$ requires 347. LC/MS purity = 100%.

**Intermediate A16 – *N*-(Tetrazol-5-ylmethyl)-4'-trifluoromethylbiphen-4-ylmethylamine**



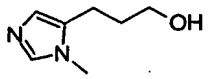
Prepared from intermediate A14 by the method of intermediate A15.

**Intermediate A17 - 3-(3-Methylimidazol-4-yl)propionic acid ethyl ester**



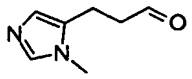
Prepared from 3-(3-Methylimidazol-4-yl)prop-2-enoic acid ethyl ester by the method of intermediate A9.

**Intermediate A18 - 3-(3-Methylimidazol-4-yl)propan-1-ol**



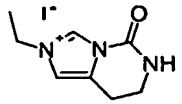
1M lithium aluminium hydride in diethyl ether (5.75ml) in dry tetrahydrofuran (10ml) was stirred in an ice bath under nitrogen and a solution of intermediate A17 (1.047g) in dry THF (10ml) added dropwise. The resultant mixture was allowed to warm to 21°C over 2h. The mixture was cooled in an ice bath and carefully treated (CARE effervescence) with water (0.43ml), 1M sodium hydroxide (0.29ml) and further water (0.66ml). The mixture was stirred for 0.33h, filtered and the solid washed with further THF. The combined filtrates were evaporated under reduced pressure to give the desired product (0.743g). $^1$H-NMR ($CDCl_3$) δ 1.8-2.0 (2H, m), 2.65 (2H, t), 3.56 (3H, s), 3.73 (2H, t), 6.78 (1H, s), 7.37 (1H, s).

**Intermediate A19 - 3-(3-Methylimidazol-4-yl)propionaldehyde**



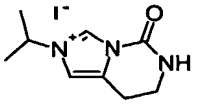
A solution of oxalyl chloride (0.553ml) in dry dichloromethane (15ml) was stirred under nitrogen and cooled to - 78°C. Anhydrous dimethyl sulphoxide (0.9ml) in dichloromethane (10ml) was added dropwise and the mixture was stirred for 0.25h. A solution of intermediate A18 (0.740g) in dry dichloromethane (10ml) was added dropwise and stirred for 0.5h. Triethylamine (3.68ml) was added to the mixture which was allowed to warm to 21°C over 3.5h. Water was added and the organic phase separated. The aqueous layer was extracted with further dichloromethane and the combined organic layers washed with brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the residue chromatographed on silica gel using cyclohexane:ethyl acetate, ethyl acetate, to methanol:dichloromethane as eluents. This gave the desired product (0.455g). $^1$H-NMR ($CDCl_3$) δ 2.87 (4H, s), 3.58 (3H, s), 6.77 (1H, s), 7.43 (1H, d), 9.85 (1H, s).

**Intermediate A20 – 2-Ethyl-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidin-2-ium iodide**

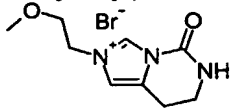


A suspension of 7,8-dihydro-6H-imidazo[1,5-c]pyrimidin-5-one in dry acetonitrile (1.3g) was stirred at room temperature and ethyl iodide (2.27ml) added. The mixture was refluxed for 16h and after cooling, the solid was filtered off, washed with acetonitrile and dried. This gave the desired product (2.08g). $^1$H-NMR (DMSO) δ 1.43 (3H, t), 3.02 (2H, t), 3.43-3.52 (2H, m), 4.24 (2H, q), 7.70 (1H, s), 9.03 (1H, br.s), 9.72 (1H, s).

Similarly prepared was:

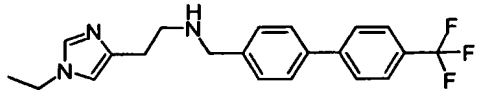
| | | |
|---|---|---|
| **Int. A21** |  | 2-Isopropyl-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidin-2-ium iodide |

**Intermediate A22 - 2-(2-Methoxyethyl)-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidin-2-ium bromide**



A suspension of 7,8-dihydro-6H-imidazo[1,5-c]pyrimidin-5-one in dry acetonitrile (1.3g) was stirred at room temperature and 2-methoxyethyl bromide (2.67ml) added. The mixture was refluxed for 16h and after cooling, the solvent was removed under reduced pressure and the residue triturated with diethyl ether. The oil remaining was dried under high vacuum to give the title compound. $^1$H-NMR (DMSO) δ 3.03 (2H, t), 3.45-3.52 (2H, m), 3.73 (2H, t), 3.28 (3H, s), 4.41 (2H, t), 7.65 (1H, br.s), 9.06 (1H, br.s), 9.69 (1H, s).

**Intermediate A23 – *N*-(2-(1-Ethylimidazol-4-yl)ethyl) 4'-trifluoromethylbiphen-4-ylmethylamine**

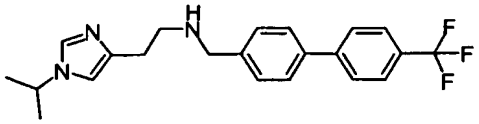


A mixture of intermediate A20 and 6M hydrochloric acid (20ml) was heated to reflux for 8h and cooled. After evaporation under reduced pressure, the residue was dissolved in water and extracted with dichloromethane. The aqueous layer was briefly evaporated under reduced pressure and passed down an IRA 400

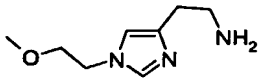
(OH) column and evaporated under reduced pressure to give an oil (0.82g). This material was dissolved in dichloromethane (100ml) and intermediate A1 (1.147g) added followed by dry 4Å molecular sieves (12g). The mixture was swirled and then stood for 3h. The mixture was filtered and the solvent removed under reduced pressure. This gave a solid that was dissolved in ethanol (25ml) and sodium borohydride (0.223g) added under nitrogen with stiring. Gentle gas evolution was observed. After 16h at room temperature, the solvent was removed under reduced pressure and the residue treated with water, basified with 2M sodium hydroxide and extracted with dichloromethane. The organic extracts were washed with dilute brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel using 5-15% methanol:ethyl acetate as eluent to give the desired material (0.92g). $^1$H-NMR ($CDCl_3$) δ 1.43 (3H, t), 2.79 (2H, t), 2.97 (2H, t), 3.87 (2H, q), 3.93 (2H, q), 6.70 (1H, s), 7.36-7.45 (3H, m), 7.55 (2H, d), 7.67 (4H, br.s); LC/MS (ESI+) found (M+1) 374; $C_{17}H_{16}F_3N_5$ requires 373. LC/MS purity = 100%.

Similarly prepared was:

**Intermediate A24 – *N*-(2-(1-Isopropylimidazol-4-yl)ethyl) 4'-trifluoromethylbiphen-4-ylmethylamine**



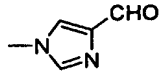
**Intermediate A25 –2-(1-(2-Methoxyethyl)-imidazol-4-yl)ethylamine**



A mixture of intermediate A22 (2.18g), diisopropylethylamine (2.75ml) and *tert.*butyl alcohol was refluxed for 48h, cooled and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane and washed with water and dried over sodium sulphate. The solvent was removed under reduced pressure to give an oil that was chromatographed on silica gel using 2-8% methanol:dichloromethane as eluents. This gave a clear oil which slowly crystallised (0.71g). This material was dissolved in dichloromethane (10ml) and trifluoroacetic acid (2ml) added with stirring. After 1h, the solvents were removed under reduced pressure. Diethyl ether was added and removed under reduced pressure. The residue was passed down an IRA 400 (OH) column eluting with water. The water was removed under reduced pressure and the

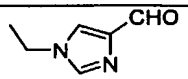
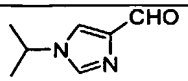
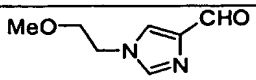
residue taken up in ethanol and the solvent removed under reduced pressure. The solid so formed was dried under vacuum to give the title compound (0.36g). $^1$H-NMR ($CDCl_3$) δ 2.69 (2H, t), 2.99 (2H, br.t), 3.34 (3H, s), 3.62 (2H, q), 4.03 (2H, q), 6.75 (1H, s), 7.43 (1H, s).

**Intermediate A26 – 1-Methylimidazole-4-carboxaldehyde**

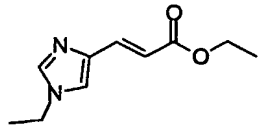


To a stirred suspension of imidazole-4-carboxaldehyde (1.0g) in dry tetrahydrofuran (60ml) under nitrogen at room temperature was added sodium hydride (60% suspension in oil, 0.437g) in small portions. The suspension was stirred until effervescence had ceased. A solution of methyl iodide (0.65ml) in THF (10ml) was added dropwise and the resulting reaction stirred at 21°C for 4h. Methanol was added and the mixture evaporated under reduced pressure to give a yellow oil which was chromatographed on silica gel using cyclohexane:ethyl acetate, ethyl acetate, to methanol:dichloromethane as eluents. This gave the desired product (0.807g). $^1$H-NMR ($CDCl_3$) δ 3.78 (3H, s), 7.58 (1H, s), 7.62 (1H, s), 9.85 (1H, s).

Similarly prepared were:

| | | |
|---|---|---|
| Intermediate A27 |  | 1-Ethylimidazole-4-carboxaldehyde |
| Intermediate A28 |  | 1-Isopropylimidazole-4-carboxaldehyde |
| Intermediate A29 |  | 1-(2-Methoxyethyl)-imidazole-4-carboxaldehyde |

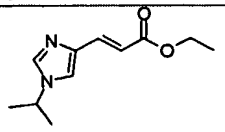
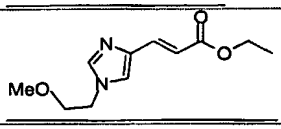
**Intermediate A110 3-(1-Ethylimidazol-4-yl)prop-2-enoic acid ethyl ester**



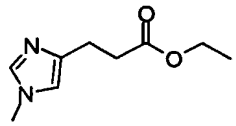
To a solution of triethylphosphonoacetate (5.16ml) in dry THF (100ml), under nitrogen and cooled with an ice bath, was added sodium hydride (1.04g) in small portions. When effervescence had ceased, a solution of intermediate A27 (2.8g) in dry tetrahydrofuran (100ml) was added dropwise. After the addition was complete, the mixture was stirred in an ice bath for a further 1h and at 21°C for 4.5h, partioned between ethyl acetate and water. The aqueous phase was extracted with further ethyl acetate and the combined organic layers washed with

further water and brine and dried over sodium sulphate. Removal of the solvent under reduced pressure gave a cream solid that was chromatographed on silica using ethyl acetate:cyclohexane, ethyl acetate, ethyl acetate:methanol as successive eluents. This gave the title compound (4.55g). $^1$H-NMR ($CDCl_3$) δ 1.32 (3H, t),1.47 (3H, t), 4.0 (2H, t), 4.23 (2H, t), 6.53 (1H, d), 7.12 (1H, d), 7.51 (1H, s), 7.56 (1H, d); LC/MS (ESI+) found (M+1) 195; $C_{10}H_{14}N_2O_2$ requires 194.

Similarly prepared were:

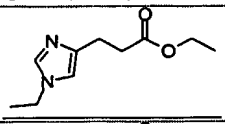
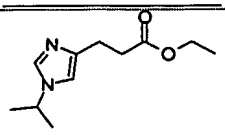
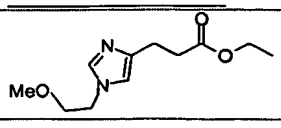
| Int. | Precursor | Structure | Name |
|---|---|---|---|
| A111 | A28 |  | 3-(1-*i*-Propylimidazol-4-yl)prop-2-enoic acid ethyl ester |
| A112 | A29 |  | 3-(1-(2-Methoxyethyl)imidazol-4-yl)prop-2-enoic acid ethyl ester |

**Intermediate A30 - 3-(1-Methylimidazol-4-yl)propionic acid ethyl ester**

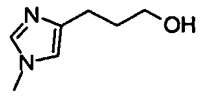


Prepared from 3-(1-methylimidazol-4-yl)prop-2-enoic acid ethyl ester by the method of intermediate A9.

Similarly prepared were:

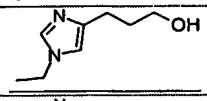
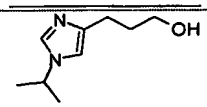
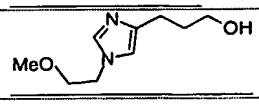
| Int. | Precursor | Structure | Name |
|---|---|---|---|
| A120 | A110 |  | 3-(1-Ethylimidazol-4-yl)propionic acid ethyl ester |
| A121 | A111 |  | 3-(1-*i*-Propylimidazol-4-yl)propionic acid ethyl ester |
| A122 | A112 |  | 3-(1-(2-Methoxyethyl)imidazol-4-yl)propionic acid ethyl ester |

**Intermediate A31 - 3-(1-Methylimidazol-4-yl)propan-1-ol**

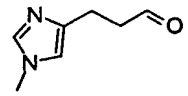


Prepared from intermediate A30 by the method of intermediate A18.

Similarly prepared were:

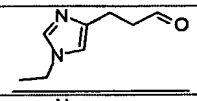
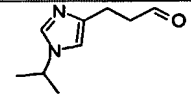
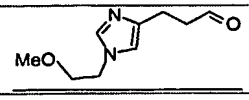
| Int. | Precursor | Structure | Name |
|---|---|---|---|
| A130 | A120 |  | 3-(1-Ethylimidazol-4-yl)propan-1-ol |
| A131 | A121 |  | 3-(1-*i*-Propylimidazol-4-yl)propan-1-ol |
| A132 | A122 |  | 3-(1-(2-Methoxyethyl)imidazol-4-yl)propan-1-ol |

**Intermediate A32 - 3-(1-Methylimidazol-4-yl)propionaldehyde**

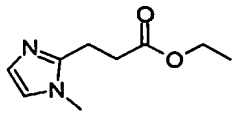


Prepared from intermediate A31 by the method of intermediate A19

Similarly prepared were:

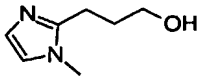
| Int. | Precursor | Structure | Name |
|---|---|---|---|
| A140 | A130 |  | 3-(1-Ethylimidazol-4-yl)propionaldehyde |
| A141 | A131 |  | 3-(1-*i*-Propylimidazol-4-yl)propionaldehyd |
| A142 | A132 |  | 3-(1-(2-Methoxyethyl)imidazol-4-yl)propionaldehyde |

**Intermediate A33 - 3-(1-Methylimidazol-2-yl)propionic acid ethyl ester**



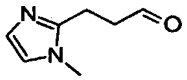
Prepared from 3-(1-methylimidazol-2-yl)prop-2-enoic acid ethyl ester by the method of intermediate A9.

**Intermediate A34 - 3-(1-Methylimidazol-2-yl)propan-1-ol**



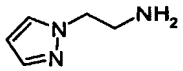
Prepared from intermediate A33 by the method of intermediate A18.

**Intermediate A35 - 3-(1-Methylimidazol-2-yl)propionaldehyde**



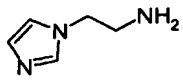
Prepared from intermediate A34 by the method of intermediate A19.

**Intermediate A36 - 2-(Pyrazol-1-yl)ethylamine hydrobromide**



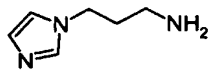
Prepared from pyrazole by the method of intermediate A6.

**Intermediate A37 - 2-(Imidazol-1-yl)ethylamine hydrobromide**



Prepared from imidazole by the method of intermediate A6.

**Intermediate A38 - 3-(Imidazol-1-yl)propylamine.hydrobromide**



Prepared from imidazole by the method of intermediate A7.

The following amines were commercially available:

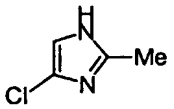
Intermediate A41 — 2-(Benzimidazol-2-yl)ethylamine
Intermediate A42 — 2-(5-Chlorobenzimidazol-2-yl)ethylamine
Intermediate A43 — Histamine

Intermediate A44 — 2-(Imidazol-2-yl)ethylamine
Intermediate A45 — 3-(Imidazol-1-yl)propylamine
Intermediate A46 — 2-(Pyrid-2-yl)ethylamine
Intermediate A47 — Pyrid-2ylmethylamine
Intermediate A48 - 2-(1-Methylimidazol-5-yl)ethylamine
Intermediate A80 – 4,5-Dichloroimidazole
Intermediate A81 – 4,5-Dichloro-2-methylimidazole
Intermediate A82 – 4-Bromoimidazole
Intermediate A83 – 4-Methylimidazole

The following amine is known in the literature

Intermediate A49 - 2-(Thiazol-2-yl)ethylamine

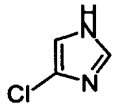
**Intermediate A84 – 4-Chloro-2-methylimidazole**



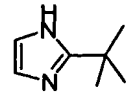

Following the general method of J. Het. Chem. 1967, 451-452. A solution of 2-methylimidazole (4.0g) in dimethylformamide (50ml) at 21°C was treated with N-chlorosuccinimide (7.03g) in dimethylformamide over 0.75h. The solution warmed on addition. After stirring overnight at room temperature, the solvent was evaporated carefully to give a brown oily solid which was chromatographed on silica using ethyl acetate:cyclohexane, dichloromethane and dichloromethane:methanol as successive eluents to give the title compound (2.75g). $^1$H-NMR ($CDCl_3$) δ 2.42 (3H, s), 6.82 (1H, s).

Similarly prepared was

**Intermediate A85 4-Chloroimidazole**

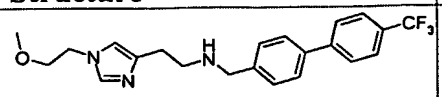
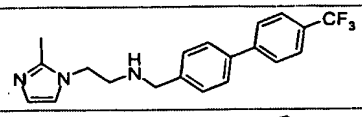
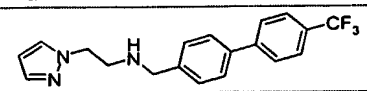
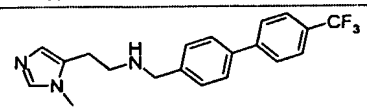
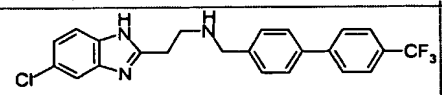
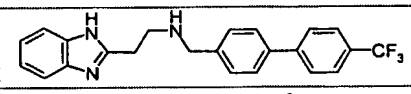
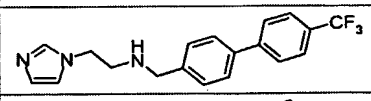
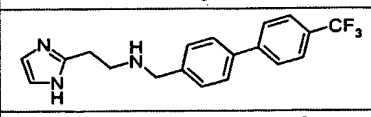
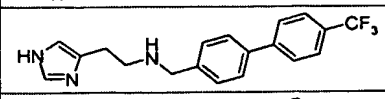
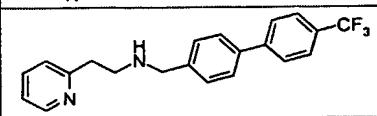
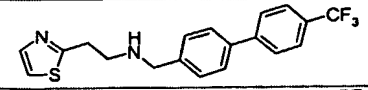
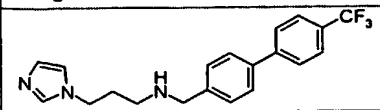
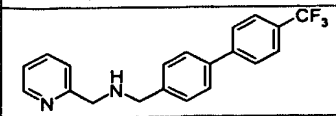


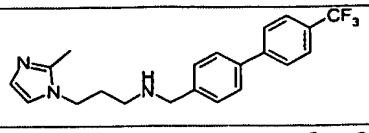
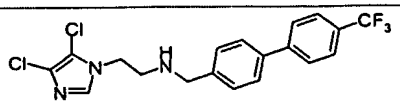
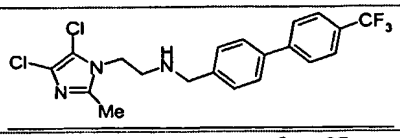
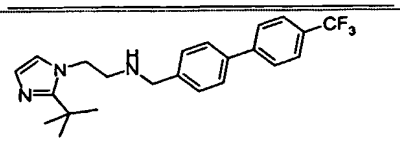
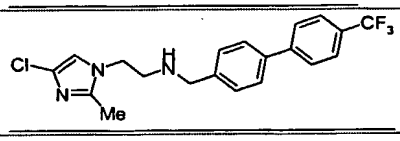

**Intermediate A86 2-*t*-Butylimidazole**



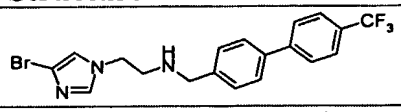
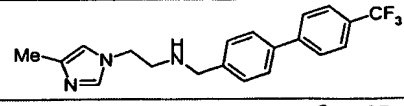
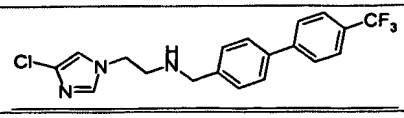

Prepared using the method of Chim Ind Milan 1972, 223 and Tetrahedron 1971, 27,3575-3579.

The following intermediates were prepared from intermediate A1 by the method of Intermediate A4:

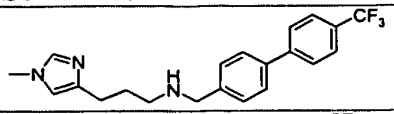
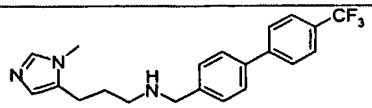
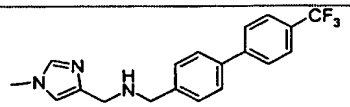
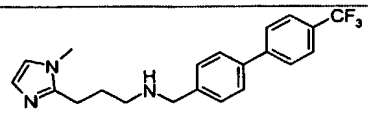
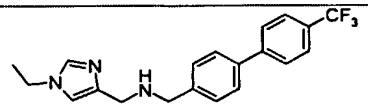
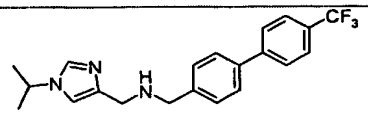
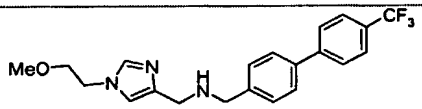
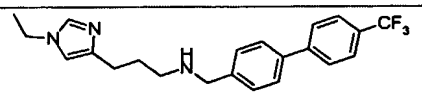
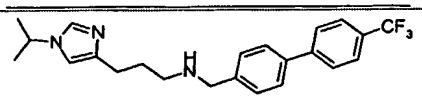
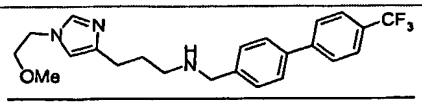
| Int. | Precursor | Structure | Name |
|---|---|---|---|
| A50 | A25 |  | N-(2-(1-(2-methoxyethyl)imidazol-4-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamine |
| A51 | A6 |  | N-(2-(2-methylimidazol-1-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A52 | A36 |  | N-(2-(pyrazol-1-yl)ethyl)-4'-trifluoro-methylbiphen-4-yl-methylamine |
| A53 | A48 |  | N-(2-(1-methylimidazol-5-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A54 | A42 |  | N-(2-(5-chlorobenzimidazol-2-yl)ethyl) 4'-trifluoromethylbiphen-4-yl-methylamine |
| A55 | A41 |  | N-(2-(benzimidazol-2-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A56 | A37 |  | N-(2-(imidazol-1-yl)ethyl)-4'-trifluoro-methylbiphen-4-yl-methylamine |
| A57 | A44 |  | N-(2-(imidazol-2-yl)ethyl)-4'-trifluoro-methylbiphen-4-yl-methylamine |
| A58 | A43 |  | N-(2-(imidazol-4-yl)ethyl)-4'-trifluoro-methylbiphen-4-yl-methylamine |
| A59 | A46 |  | N-(2-(pyrid-2-yl)ethyl)-4'-trifluoro-methylbiphen-4-yl-methylamine |
| A60 | A49 |  | N-(2-(thiazol-2-yl)ethyl)-4'-trifluoro-methylbiphen-4-yl-methylamine |
| A61 | A38 |  | N-(3-(imidazol-1-yl)propyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A62 | A47 |  | N-(pyrid-2-ylmethyl)-4'-trifluoro-methylbiphen-4-yl-methylamine |

| | | | |
|---|---|---|---|
| A63 | A7 |  | N-(3-(2-methylimidazol-1-yl)propyl)-4'-trifluoromethylbiphen-4-yl-methylamine |
| A100 | A90 |  | N-(2-(4,5-Dichloroimidazol-1-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamine |
| A101 | A91 |  | N-(2-(4,5-Dichloro-2-methylimidazol-1 yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamine |
| A102 | A92 |  | N-(2-(2-*t*-Butylimidazol-1-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A103 | A95 |  | N-(2-(4-Chloro-2-methylimidazol-1-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamine |

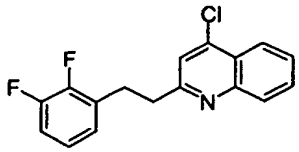
The following intermediates were also prepared from intermediate A1 by the method of A4 except that the purification of the required imidazole isomer was completed with a crystallisation step. For intermediate A104, light petrol was used. For intermediate A105, several crystallisations were used in a sequential manner - light petroleum/ethyl acetate followed by ethyl acetate and finally light petroleum/*n* butyl acetate. For intermediate A106, ethyl acetate/light petrol was used.

| **Int.** | **Precursor** | **Structure** | **Name** |
|---|---|---|---|
| A104 | A93 |  | N-(2-(4-Bromoimidazol-1-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A105 | A94 |  | N-(2-(4-Methylimidazol-1-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A106 | A96 |  | N-(2-(4-Chloroimidazol-1-yl)ethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |

The following intermediates were prepared from intermediate A3 by the method of Intermediate A5:

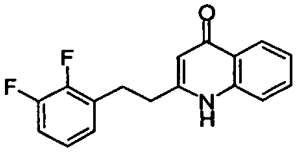
| Int. | Precursor | Structure | Name |
|---|---|---|---|
| A65 | A32 |  | N-(3-(1-methylimidazol-4-yl)propyl)-4' trifluoromethylbiphen-4-yl-methylamin |
| A66 | A19 |  | N-(3-(1-methylimidazol-5-yl)propyl)-4' trifluoromethylbiphen-4-yl-methylamin |
| A67 | A26 |  | N-((1-methylimidazol-4-yl)methyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A68 | A35 |  | N-(3-(1-methylimidazol-2-yl)propyl)-4' trifluoromethylbiphen-4-yl-methylamin |
| A69 | A27 |  | N-(1-ethylimidazol-4-ylmethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A70 | A28 |  | N-(1-isopropylimidazol-4-ylmethyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A71 | A29 |  | N-(1-(2-methoxyethyl)imidazol-4-ylmethyl)-4'-trifluoromethylbiphen-4-yl methylamine |
| A150 | A140 |  | N-(3-(1-ethylimidazol-4-yl)propyl)-4'-trifluoromethylbiphen-4-yl-methylamin |
| A151 | A141 |  | N-(3-(1-*i*-propylimidazol-4-yl)propyl)-4 trifluoromethylbiphen-4-yl-methylamin |
| A152 | A142 |  | N-(3-(1-(2-methoxyethyl)imidazol-4-yl)propyl)-4'-trifluoromethylbiphen-4-y methylamine |

**Intermediate B1 — 4-Chloro-2-(2-(2,3-difluorophenyl)ethyl)quinoline**



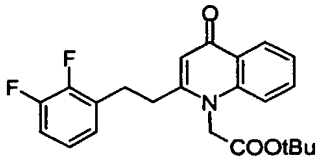
Butyllithium (4.76ml, 2.5M in hexanes, 1 equiv) was added dropwise to a solution of 4-chloroquinaldine (2.4ml, 1 equiv) in tetrahydrofuran (30ml) at –78°C and the reaction mixture stirred for 15min. 2,3-Difluorobenzyl bromide (1.82ml, 1.2 equiv) was added dropwise and stirring was continued for 1h. After warming to room temperature the solution was diluted with water and ethyl acetate and the organic phase dried and evaporated. Chromatography (silica, 10:1 petrol / ethyl acetate) gave the title compound as a white solid (3.16g). $^1$H-NMR ($CDCl_3$) δ 3.23 (4H, m), 6.89-6.99 (3H, m), 7.33 (1H, s), 7.59 (1H, m), 7.74 (1H, m), 8.04 (1H, d), 8.15 (1H, d); MS (APCI+) found (M+1) = 304; $C_{17}H_{12}{}^{35}ClF_2N$ requires 303.

**Intermediate B2 — 2-(2-(2,3-Difluorophenyl)ethyl)-1*H*-quinolin-4-one**



4-Chloro-2-(2,3-difluorophenylethyl)quinoline (Int. B1) (2.83g) was heated to reflux in aqueous hydrochloric acid (2M, 15ml) and dioxane (6ml) for 72h. The reaction mixture was extracted with dichloromethane (90ml) and methanol (10ml), and the organic phase dried and evaporated to give the title compound as a white solid (2.61g). $^1$H-NMR ($d_6$-DMSO) δ 3.15 (4H, s), 6.46 (1H, s), 7.15 (2H, m), 7.27 (1H, m), 7.51 (1H, m), 7.82 (2H, m), 8.15 (1H, d); MS (APCI+) found (M+1) = 286; $C_{17}H_{13}F_2NO$ requires 285.

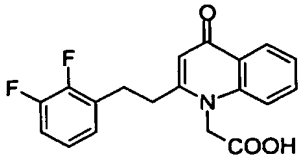
**Intermediate B3 — *Tert* butyl [2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4*H*-quinolin-1-yl]acetate**



To a slurry of 2-(2-(2,3-difluorophenyl)ethyl)-1*H*-quinolin-4-one (Int. B2) (33g) in dry THF (500ml) at 0°C under argon was added dropwise *n*-butyl lithium (2.5M in hexanes) (47ml). The solid dissolved during the addition. The mixture was allowed to warm to room temperature and stirred at this temperature for 0.5h. *Tert.* butyl bromoacetate (28ml) was added and the mixture heated at 40°C for 48h. The mixture was cooled to room temperature and poured into saturated ammonium chloride and extracted with dichloromethane (x3). The combined extracts were washed with brine, dried over magnesium sulphate and evaporated under reduced pressure to give a brown solid. Trituration of this material with

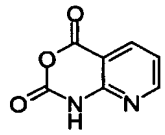
hexane and then diethyl ether gave the title compound (35.7g). 1H NMR ($CDCl_3$) δ 1.46 (9H, s), 2.85-3.15 (4H, m), 4.83 (2H, s), 6.25 (1H, s), 6..8-7.2 (3H, m), 7.2-7.45 (2H, m), 7.6-7.7 (1H, m), 8.4-8.5 (1H, m).

**Intermediate B4 — [2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl]acetic acid**



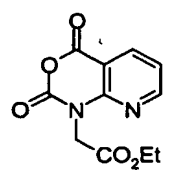

To a solution of *tert* butyl [2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4*H*-quinolin-1-yl]acetate (Int. B3) (35g) in dry dichloromethane (300ml) was added trifluoroacetic acid (50ml) and the solution left for 68h. The mixture was evaporated under reduced pressure to give an oily gum which was triturated with diethyl ether. The solid so formed was washed with water and dried under vacuum. This gave the desired material (30g). $^1$H-NMR ($d_6$-DMSO) δ 2.8–3.2 (4H, m), 5.24 (2H, s), 6.19 (1H, s), 7.05-7.4 (3H, m), 7.4-7.55 (1H, m), 7.55-7.9 (2H, m), 8.15-8.3 (1H,m)

**Intermediate C1 — 3-Azaisatoic anhydride**




To a stirring solution of 2,3-pyridinedicarboxylic anhydride (100g, 1 equiv) in anhydrous tetrahydrofuran (1L) was added dropwise under argon at 38-46°C over 1.25h azidotrimethylsilane (97.9 ml, 1.1 equiv). The temperature was maintained at 45-50°C for a further 2h then the mixture refluxed for 30 min, cooled to ambient temperature and ethanol (43 ml, 1.1 equiv) added dropwise. On stirring for 16h an off-white solid was obtained which was filtered, washed and dried, to give the title compound (90.7g). $^1$H-NMR ($d_6$-DMSO) δ 7.25-7.35 (1H, m), 8.30-8.35 (1H, dd), 8.65-8.7 (1H, dd), 11.3 (1H, br s).

**Intermediate C2 — Ethyl (2,4-dioxo-4*H*-pyrido[2,3-*d*][1,3]oxazin-1-yl)acetate**

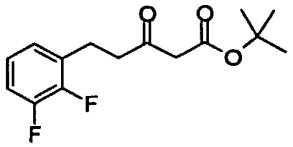


A 2:1 mixture of 3- and 6-azaisatoic anhydride (3.55 g, 21.6 mmol) (*Synthesis* **1982**, *11*, 972) was added portionwise to a suspension of sodium hydride (0.95 g, 60% in oil, 23.8 mmol) in DMF (40 ml). After stirring for 1h, ethyl bromoacetate (2.64 ml, 23.8 mmol) was added. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure. Ice/water was added to the residue and stirred for 1h. The resulting pink solid was collected by filtration, washed with water and dried under vacuum at 40°C. The product was a 4:1 mixture of the [2,3-*d*] and the [3,2-*d*] isomers. $^1$H-NMR data of the title compound. $^1$H-NMR ($d_6$-DMSO) δ 1.21 (3H,t), 4.18 (2H,q), 4.92 (2H,s), 7.45 (1H,dd), 8.47 (1H,dd), 8.77 (1H,dd); MS (APCI+) found (M+1) = 251; $C_{11}H_{10}N_2O_5$ requires 250.

The title compound could also be prepared by the following method:

To a stirring mixture of 3-azaisatoic anhydride (Int. C1) (84.36g, 1 equiv) and N,N-diisopropylethylamine (94 ml, 1.05 equiv) in N-methylpyrrolidone (420 ml) was added dropwise under argon at 45-50°C, ethyl bromoacetate (57 ml, 1 equiv). After 16h at 50°C the mixture was cooled (ice bath) and water (560 ml) added with vigorous stirring. The solid which precipitated was filtered, washed with water and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. An insoluble solid was filtered off and discarded and the ethyl acetate layer washed again with saturated sodium bicarbonate, dried ($Na_2SO_4$) and evaporated. The residue was triturated with a 1:1 mixture of ether / light petrol, filtered, washed and dried to give the title compound as an off-white solid, yield (56.0g).

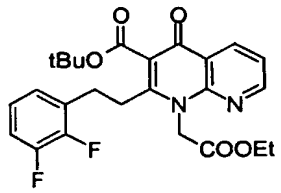
**Intermediate C3 — 5-(2,3-Difluorophenyl)-3-oxopentanoic acid *tert*-butyl ester**




To an ice cooled stirring suspension of sodium hydride (1.96 g, 49.1 mmol, 60% dispersion in oil) in dry tetrahydrofuran (100 ml) was added dropwise under an argon atmosphere *tert*-butylacetoacetate (7.4 ml, 44.6 mmol). After a further 15 min, *n*-butyllithium(18.7 ml, 46.8 mmol, 2.5M in hexanes) was added dropwise maintaining the reaction temperature below 10°C. 2,3-Difluorobenzyl bromide (11.08 g, 53.5 mmol) was added dropwise 20 min later, then the mixture allowed to warm to ambient temperature. After a further 15 min the reaction mixture was poured onto a mixture of water (150 ml) and glacial acetic acid (10 ml), extracted 3 times with ethyl acetate and the combined extracts washed with saturated

sodium hydrogen carbonate then brine, dried ($MgSO_4$) and evaporated to a yellow oil. Chromatography (fine silica, ethyl acetate-light petrol) gave the title compound as a yellow oil, yield 9.05 g (71%). 1H NMR ($CDCl_3$) δ 1.45 (9H, s), 2.84-2.91 (2H, m), 2.95-3.00 (2H, m), 3.35 (2H, s), 6.92-7.04 (3H, m).

**Intermediate C4 — (3-*tert*-Butoxycarbonylmethyl-2-[2-(2,3-difluorophenyl)ethyl]-4-oxo-4*H*-[1,8]naphthyridin-1-yl)acetic acid ethyl ester**

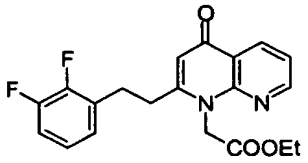



To a stirring suspension of sodium hydride (562 mg, 14.06 mmol, 60% dispersion in oil) in dry DMF (50 ml) was added dropwise 5-(2,3-difluorophenyl)-3-oxopentanoic acid *tert*-butyl ester (Int. C3) (3.63 g, 12.78 mmol). After 10 min, ethyl (2,4-dioxo-4*H*-pyrido[2,3-*d*][1,3]oxazin-1-yl)acetate (Int. C2) (3.21 g, 12.78 mmol) was added and the mixture stirred for 16h. The solvent was evaporated and the residue treated with saturated aq. ammonium chloride and extracted 3 times with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. Chromatography (fine silica, ethyl acetate-light petrol) gave the title compound as a light brown solid, yield 1.88g (31%). 1H NMR (d6-DMSO) δ 1.31 (3H, t), 1.63 (9H, s), 2.95-3.03 (2H, m), 3.08-3.13 (2H, m), 4.27 (2H, q), 5.31 (2H, s), 7.01-7.11(3H, m), 7.35-7.38 (1H, m), 8.67-8.71 (2H, m).

The title compound was also made by the following method:

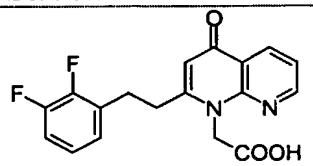
To an ice-cooled solution of intermediate C2 (55.9g, 1 equiv) and intermediate C3 (63.5 g, 1 equiv) in dichloromethane (700 ml) was added dropwise under argon over 45 min 1,8-diazabicyclo[5.4.0]undec-7-ene (40 ml, 1.2 equiv). After 1h the ice bath was removed and after a further 2.5h the mixture was washed with saturated aqueous ammonium chloride, dried ($Na_2SO_4$) and evaporated. The crude product was chromatographed (fine silica, ethyl acetate-dichloromethane) then triturated with light petrol to give the title compound (80.27g).

**Intermediate C5 — (2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-4*H*-[1,8]naphthyridin-1-yl)acetic acid ethyl ester**



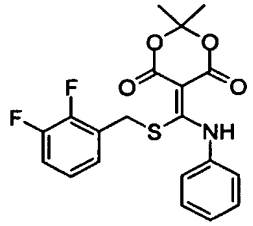

(3-*tert*-Butoxycarbonylmethyl-2-[2-(2,3-difluorophenyl)ethyl]-4-oxo-4*H*-[1,8]naphthyridin-1-yl)acetic acid ethyl ester (Int C4) (1.35 g, 2.86 mmol) was added portionwise to boiling diphenyl ether (10 ml) with stirring. After 20 min, the dark solution was allowed to cool to ambient temperature. Petroleum ether (b.p. 60-80) was added to the point of cloudiness to give the product as a crystalline solid, yield 724 mg (68%). $^1$H NMR (d6-DMSO) δ 1.19 (3H, t), 3.02-3.09 (4H, m), 4.16 (2H, q), 5.31 (2H, s), 6.10 (1H, s), 7.13-7.21 (2 H, m), 7.26-7.33 (1H, m), 7.46-7.49 (1H, m), 8.49 (1H, m), 8.76 (1H, m). MS (APCI+), found (M+1) = 373, $C_{20}H_{18}F_2N_2O_3$ requires 372.

The following intermediates were prepared by the method of Intermediate D4:

| No. | Precursor | Structure | Name |
|---|---|---|---|
| C6 | C5 |  | (2-[2-(2,3-difluorophenyl)ethyl]-4-oxo-4*H*-[1,8]naphthyridin-1-yl)acetic acid |



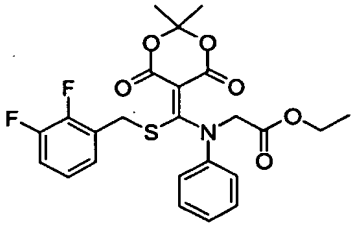
**Intermediate D1 — 5-(1-(2,3-Difluorobenzylthio)-1-phenylaminomethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione**




To hexane washed sodium hydride (7.45g, 60% in oil) under argon, was added N-methylpyrrolidone (NMP) (270ml) and the mixture cooled in an ice-salt bath. 2,2-Dimethyl-1,3-dioxane-4,6-dione (26.8g) was added portionwise over 20min keeping the temperature between 5-10°C. Effervescence was noted during the addition. The mixture was stirred at room temperature for 1h and phenylisothiocyanate (25.2g) added over 15min. The mixture was stirred at room temperature for 2.5h and cooled to 15°C in a cold water bath. 2,3-Difluorobenzyl

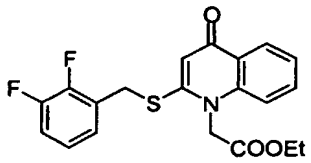
bromide (38.6g) was added over 10min and stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate (1.2L) and water. The organic layer was washed with further water and then brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue triturated with 40-60°C petrol and the solid collected by filtration. Crystallisation from methyl *t*.butyl ether gave the title compound as a pale yellow solid (51.4g). $^1$H-NMR ($d_6$-DMSO) δ 1.64 (6H, s), 4.16 (2H, d), 7.1-7.25 (2H, m), 7.25-7.5 (6H, m), 12.12 (1H, br s); MS (APCI-) found (M-1) = 404; $C_{20}H_{17}F_2NO_4S$ requires 405.

**Intermediate D2 — Ethyl 2-(1-(2,3-difluorobenzylthio)-1-(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene)-methyl)phenylamino)acetate**



To hexane washed sodium hydride (1.0g, 60% in oil) under argon, was added NMP (30ml). A solution of 5-(1-(2,3-difluorobenzylthio)-1-phenylaminomethylene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (10.0g) (intermediate D1) in NMP (20ml) was added by syringe over 15min at room temperature and stirred for 30min. Ethyl bromoacetate (4.5g) was added and the mixture heated at 60°C for 6h. The mixture was partitioned between ethyl acetate and water and the aqueous layer extracted with further ethyl acetate. The combined organic layers were washed with further water and brine, dried over $MgSO_4$, and the solvent removed under reduced pressure. The orange oil so obtained was triturated with diethyl ether/ 40-60°C petrol to give a solid that was collected by filtration. This solid was recrystallised from methyl *t*-butyl ether to give the title compound (7.37g). $^1$H-NMR ($d_6$-DMSO) δ 1.24 (3H, t), 1.55 (6H, br s), 4.19 (2H, q), 4.37 (2H, d), 4.81 (2H, br s), 6.85-7.5 (8H, 2xm).

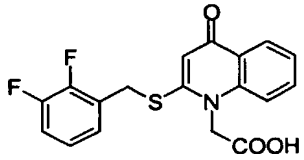
**Intermediate D3 – Ethyl (2-(2,3-difluorobenzylthio)-4-oxo-4*H*-quinolin-1-yl)acetate**



Ethyl (1-(2,3-difluorobenzylthio)-1-(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene)methyl)phenylamino)acetate (intermediate D2) (0.85g) under argon was

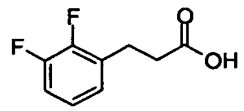
stirred with trifluoroacetic (10ml) at room temperature overnight. The mixture was evaporated under reduced pressure, dissolved in dichloromethane, washed with sodium bicarbonate solution and dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue triturated with diethyl ether to give the title compound (0.43g). $^1$H-NMR ($CDCl_3$) δ 1.27 (3H, t), 4.26 (2H, q), 4.29 (2H, s), 5.1 (2H, br s), 6.45 (1H, s), 6.95-7.25 (4H, m), 7.39 (1H, t), 7.64 (1H, dt), 8.42 (1H, dd); MS (APCI+) found (M+1) = 418; $C_{22}H_{21}F_2NO_3S$ requires 417.

**Intermediate D4 — [2-(2,3-Difluorobenzylthio)-4-oxo-4*H*-quinolin-1-yl]acetic acid**



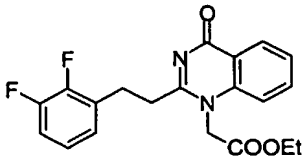

To a solution of Int. D3 (21.56g, 0.055mol) in dioxan (200ml) was added sodium hydroxide (6.0g, 0.15mol) in water (200ml) and the solution stirred for 2.5h then concentrated. The residues were dissolved in water and acidified to pH 2 with 2M hydrochloric acid and the precipitate collected and washed sequentially with water, ether and then hexane. The solids were dried *in vacuo* at 40°C to provide the title compound (20.0g, 100%). $^1$H-NMR ($d_6$-DMSO) δ 4.5 (2H, s), 5.2 (2H, br s), 6.3 (1H, s), 7.18 (1H, m), 7.3 (1H, m), 7.4 (2H, m), 7.6 (1H, d, J=8.5Hz), 7.7 (1H, t, J=8Hz), 8.1 (1H, d, J=8Hz). MS (APCI+) found (M+1) = 362;. $C_{18}H_{13}F_2NO_3S$ requires 361.

**Intermediate E1 — 3-(2,3-Difluorophenyl)propionic acid**



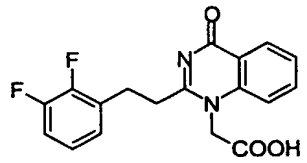

A solution of 2,3-difluorocinnamic acid (9.14g) in ethanol (250ml) with 10% palladium/carbon catalyst was hydrogenated for 5h at room temperature and atmospheric pressure. The reaction mixture was filtered through celite and concentrated *in vacuo* to give the title compound as a colourless solid (9.05g, quant.) $^1$H-NMR ($CDCl_3$) δ 2.70 (2H, t), 3.02 (2H, t) and 7.01 (3H, m).

**Intermediate E2 — Ethyl 2-(2-[2-(2,3-difluorophenyl)ethyl]-4-oxo-4*H*-quinazolin-1-yl)acetate**



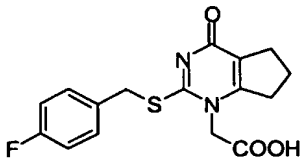

To a solution of 3-(2,3-difluorophenyl)propionic acid (Int. E1) (5g, 26.88mmol) in anhydrous dichloromethane (50ml) containing a few drops of DMF was added oxalyl chloride (4.7ml, 53.84mmol) at 0°C under argon. The solution was then stirred at ambient temperature for 2h and the solvent removed *in vacuo*. The residue which contained the acid chloride was dissoved in toluene (50ml) and added to a slurry of (2-carbamoylphenylamino)acetic acid ethyl ester (5.0g, 22.52mmol) in toluene (50ml) containing pyridine (1ml) and 4-dimethylaminopyridine (DMAP) (100mg). After 16h at 90°C the solvent was evaporated and the solid residue washed with water, aqueous ammonia and ether to give the title compound (6.9g, 82%) as a cream solid. $^1$H-NMR (DMSO) δ 1.24 (3H, t), 3.13 (2H, t), 3.34 (2H, m), 4.24 (2H, q), 5.48 (2H, s), 7.19 (1H, m), 7.29-7.35 (2H, m), 7.60-7.72 (2H, m), 7.94 (1H, t), 8.19 (1H, d); MS (APCI+) found (M+1) = 373; $C_{20}H_{18}F_2N_2O_3$ requires 372.

**Intermediate E3 — 2-(2-(2-(2,3-Difluorophenyl)ethyl)-4-oxo-4*H*-quinazolin-1-yl)acetic acid**



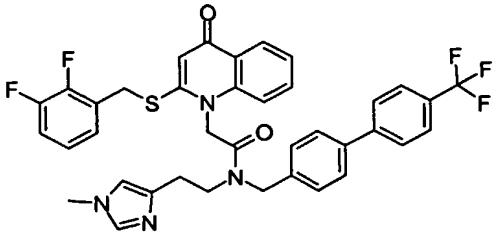

A solution of ethyl 2-(2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4*H*-quinazolin-1-yl)-acetate (Int. E2) (6.8g, 18.3mmol) in methanol (30ml) and 2M sodium hydroxide solution (18.0ml, 36mmol) was stirred at ambient temperature overnight. The solvent was removed *in vacuo* and the residue dissolved in water (10ml). Acidification to pH 1 with 2M hydrochloric acid gave a solid that was filtered, washed with water and dried *in vacuo* to give the desired product (5.9g, 94%) as a white solid. $^1$H-NMR (DMSO) δ 3.11-3.30 (4H, m), 5.31 (2H, s), 7.16-7.33 (3H, m), 7.61 (1H, t), 7.68 (1H,d), 7.89 (1H,t), 8.18 (1H,d); MS (APCI+) found (M+1) = 345; $C_{18}H_{14}F_2N_2O_3$ requires 344.

**Intermediate F1 — 2-[2-(4-Fluorobenzylthio)- 5,6-trimethylene-4-oxo-4H-pyrimidin-1-yl]acetic acid**



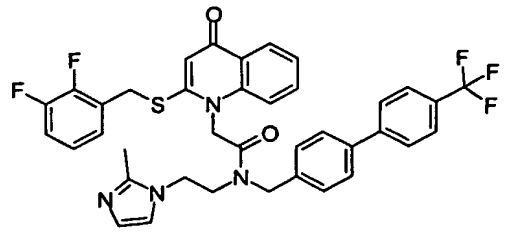

The preparation of this intermediate was described in International Application WO 01/60805 A1 incorporated herein by reference.

**Example 1 — N-(2-(1-Methylimidazol-4-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)acetamide bitartrate**



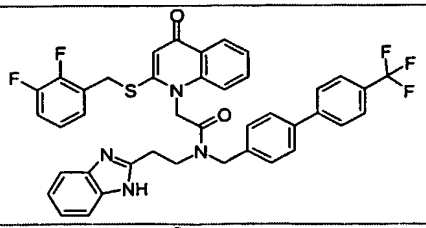
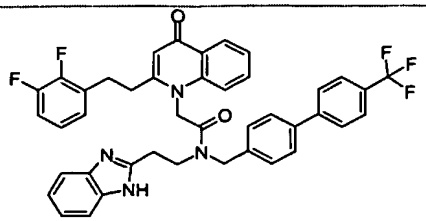
A mixture of 2-(2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)acetic acid (Int. D4) (0.101g), *N* (2-(1-methylimidazol-4-yl)ethyl)-4'-trifluoromethylbiphen-4-ylmethylamine (Int. A4) (0.10g,), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.103g) and N,N-diisopropylethylamine (0.12ml) in dimethylformamide (20 ml) was stirred at room temperature for 2h, diluted with dichloromethane and washed with saturated sodium bicarbonate and water. The organic layer was dried (anhydrous potassium carbonate) and evaporated under reduced pressure to give the free base of the title compound. $^1$H-NMR ($CDCl_3$) δ 2.85-3.0 (2H, m), 3.58 + 3.63 (3H, 2xs), 3.75-3.95 (2H, m), 4.22 + 4.24 (2H, 2xs), 4.6-4.8 (2H, br.s), 5.12 + 5.28 (2H, br.s), 6.40 (1H, s), 6.65 + 6.69 (1H, 2xs), 6.80 + 6.83 (1H, 2xs), 6.9-7.2 (3H, m), 7.2-7.8 (11H, m), 8.3-8.45 (1H, m); MS (APCI+) found (M+1) = 703; $C_{38}H_{31}F_5N_4O_2S$ requires 702. The residue was chromatographed on silica gel using , 5% 2M ammonia in methanol:dichloromethane) to give a material which was dissolved in methanol and tartaric acid (0.033g) was added. The mixture was stirred for 0.17h and the solvent removed under reduced pressure. The residue was triturated with diethyl ether to give the desired product (0.15g). $^1$H-NMR (DMSO) δ 2.7-2.95 (2H, m), 3.58 + 3.60 (3H, 2xs), 3.65-3.8 (2H, m), 4.29 (2H, s), 4.45-4.9 (4H, m), 5.25-5.5 (2H, m), 6.22 + 6.27 (1H, 2xs), 6.91 + 6.93 (1H, 2xbr.s), 7.05-7.5 (7H, m), 7.55-7.75 (4H, m), 7.75-7.95 (4H, m), 8.12 + 8.15 (1H, dd); MS (APCI+) found (M+1) = 703; $C_{38}H_{31}F_5N_4O_2S$ requires 702.

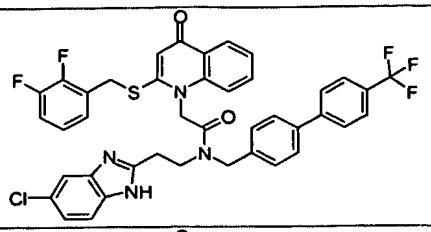
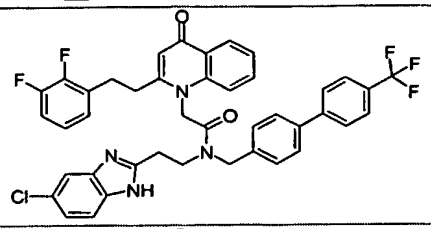
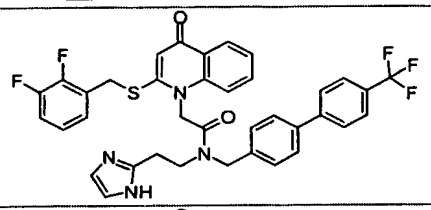
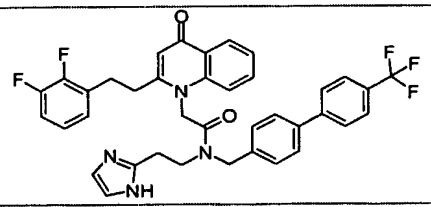
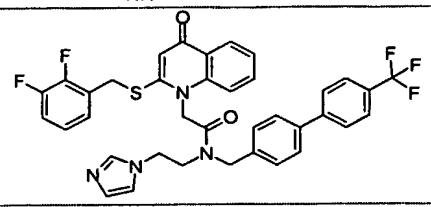
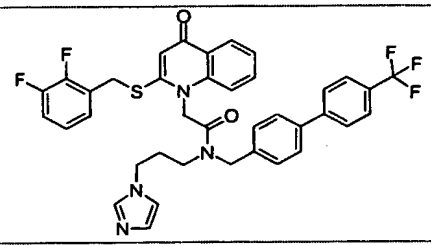
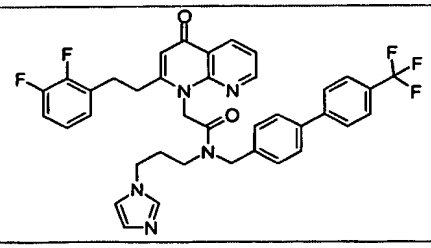
**Example 2 — N-(2-(2-Methylimidazol-1-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)acetamide**



A mixture of 2-(2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl)acetic acid (Int. D4) (0.483g), *N* (2-(2-methylimidazol-1-yl)ethyl)-4'-trifluoromethylbiphen-4-ylmethylamine (Int. A51) (0.40g,), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.48g) and N,N-diisopropylethylamine (0.543ml) in dimethylformamide (10 ml) was stirred at room temperature for 2h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The water layer was extracted with further ethyl acetate and the combined organic layers washed with 2M sodium hydroxide and brine. The solution was dried over sodium sulphate, evaporated under reduced pressure, chromatographed on silica gel using 5-15% 2M ammonia in methanol:ethyl acetate, then 2-10% methanol:methylene chloride and triturated with a mixture of ethyl acetate and light petrol to give the desired product (0.32g). $^1$H-NMR ($CDCl_3$) δ 2.37 + 2.43 (3H, m), 3.65-3.85 (2H, m), 4.14 (2H, t), 4.2-4.35 (4H, m), 4.55-5.3 (2H, br.), 6.43 + 6.48 (1H, 2xs), 6.7-7.2 (6H, 2xs), 7.2-7.4 (3H, 2xs), 7.5-7.8 (7H, m), 8.3-8.45 (1H, m); LC/MS (LC conditions: 3.3cm x 4.6mm ID, 3μM ABZ+PLUS column using a gradient system 0.1%formic acid in 10mM ammonium acetate:95% acetontrile with 0.05% formic acid, flow rate 3ml/min, injection volume 5μl), (ESI+) found (M+1) 703; $C_{38}H_{31}F_5N_4O_2S$ requires 702. LC/MS purity = 100%.

The following Examples were made by the general method of Examples 1 and/or 2:

| Ex. No. | Precursors | Structure | Name |
|---|---|---|---|
| 3 | Int. A55<br>Int. D4 |  | N-(2-(benzimidazol-2-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide bitartrate |
| 4 | Int. A55<br>Int. B4 |  | N-(2-(benzimidazol-2-yl)ethyl)-2-[2-(2(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide bitartrate |

| | | | |
|---|---|---|---|
| 5 | Int. A54<br>Int. D4 |  | N-(2-(5-chlorobenzimidazol-2-yl)ethyl 2-[2-(2,3-difluorobenzylthio)-4-oxo-4H quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide bitartrate |
| 6 | Int. A54<br>Int. B4 |  | N-(2-(5-chlorobenzimidazol-2-yl)ethyl 2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide bitartrate |
| 7 | Int. A57<br>Int. D4 |  | N-(2-(imidazol-2-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide bitartrate |
| 8 | Int. A57<br>Int. B4 |  | N-(2-(imidazol-2-yl)ethyl)-2-[2-(2-(2,3 difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide bitartrate |
| 9 | Int. A56<br>Int. D4 |  | N-(2-(imidazol-1-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 10 | Int. A61<br>Int. D4 |  | N-(3-(imidazol-1-yl)propyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 11 | Int. A61<br>Int. C6 |  | N-(3-(imidazol-1-yl)propyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |

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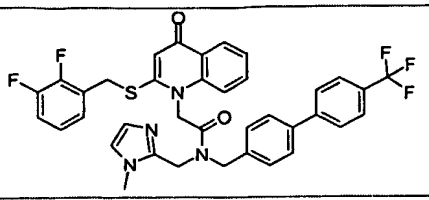
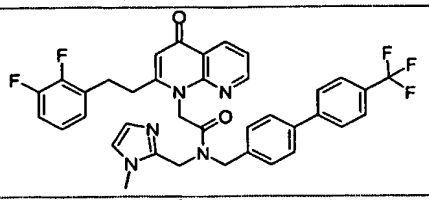
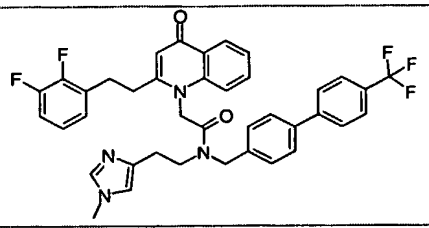
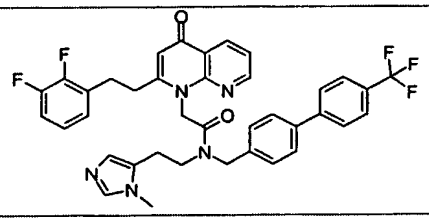
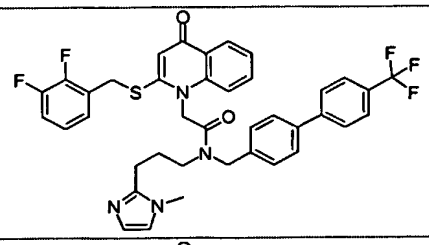
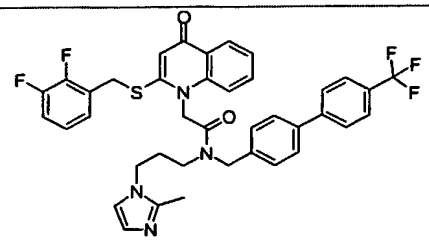
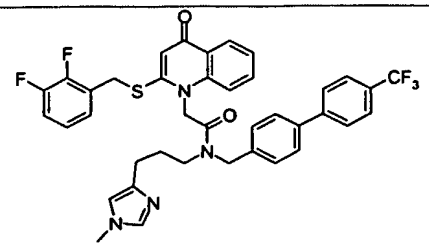
|---|---|---|---|
| 12 | Int. A5<br>Int. D4 |  | N-(1-methylimidazol-2-ylmethyl)-2-[2 (2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| 13 | Int. A5<br>Int. C6 |  | N-(1-methylimidazol-2-ylmethyl)-2-[2 (2-(2,3-difluorophenyl)ethyl)-4-oxo-4H [1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |
| 14 | Int. A4<br>Int. B4 |  | N-(2-(1-methylimidazol-4-yl)ethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-quinolin-1-yl]-N-(4'-trifluoromethy biphen-4-ylmethyl)acetamide bitartrate |
| 15 | Int. A53<br>Int. C6 |  | N-(2-(1-methylimidazol-5-yl)ethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 16 | Int. A68<br>Int. D4 |  | N-(3-(1-methylimidazol-2-yl)propyl)-2 [2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| 17 | Int. A63<br>Int. D4 |  | N-(3-(2-methylimidazol-1-yl)propyl)-2 [2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| 18 | Int. A65<br>Int. D4 |  | N-(3-(1-methylimidazol-4-yl)propyl)-2 [2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |

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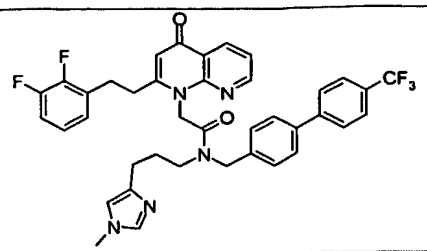
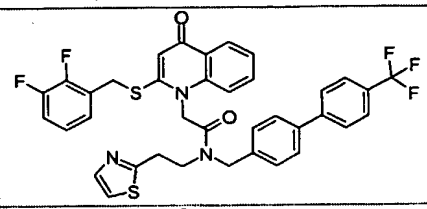
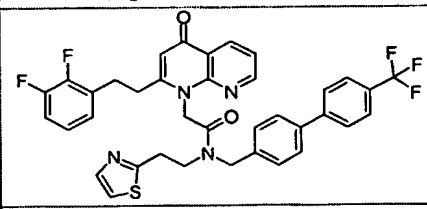
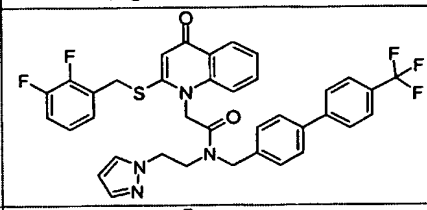
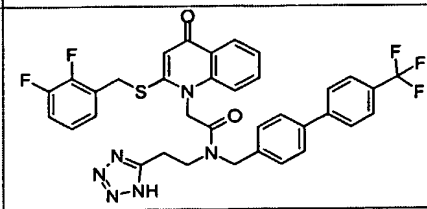
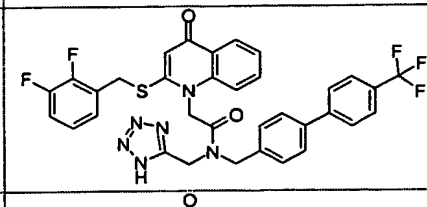
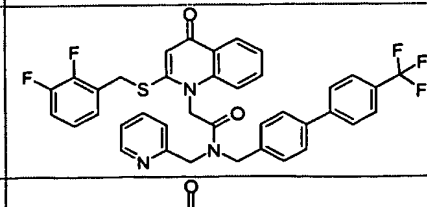
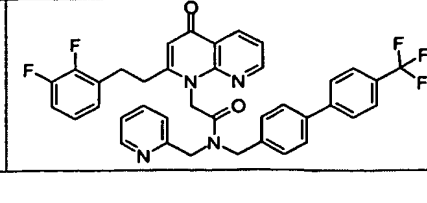
|---|---|---|---|
| 19 | Int. A65<br>Int. C6 |  | N-(3-(1-methylimidazol-4-yl)propyl)-2 [2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 20 | Int. A60<br>Int. D4 |  | N-(2-(thiazol-2-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 21 | Int. A60<br>Int. C6 |  | N-(2-(thiazol-2-yl)ethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |
| 22 | Int. A52<br>Int. D4 |  | N-(2-(pyrazol-1-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 23 | Int. A15<br>Int. D4 |  | N-(2-(tetrazol-5-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 24 | Int. A16<br>Int. D4 |  | N-(tetrazol-5-ylmethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 25 | Int. A62<br>Int. D4 |  | N-(pyrid-2-ylmethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 26 | Int. A62<br>Int. C6 |  | N-(pyrid-2-ylmethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |

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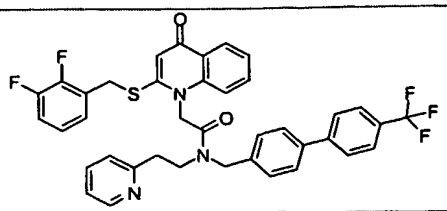
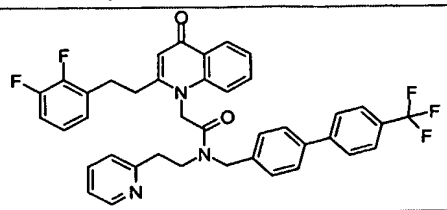
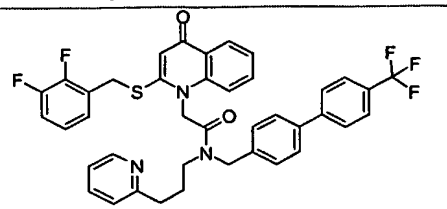
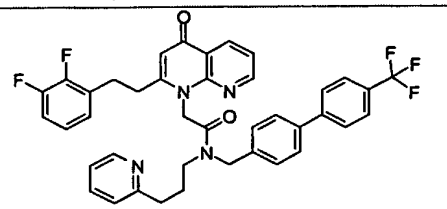
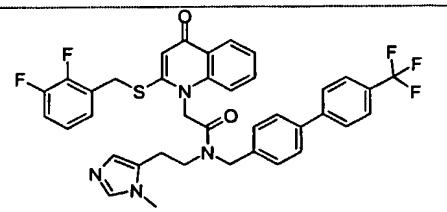
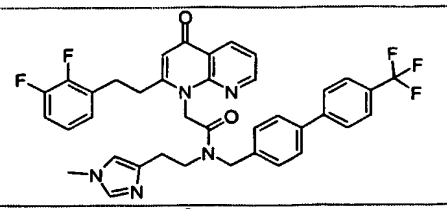
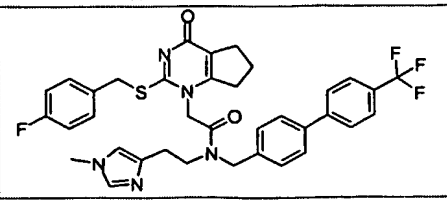
|---|---|---|---|
| **27** | Int. A59<br>Int. D4 |  | N-(2-(pyrid-2-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide bitartrate |
| **28** | Int. A59<br>Int. B4 |  | N-(2-(pyrid-2-yl)ethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide bitartrate |
| **29** | Int. A10<br>Int. D4 |  | N-(3-(pyrid-2-yl)propyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| **30** | Int. A10<br>Int. C6 |  | N-(3-(pyrid-2-yl)propyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |
| **31** | Int. A53<br>Int. D4 |  | N-(2-(1-methylimidazol-5-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| **32** | Int. A4<br>Int. C6 |  | N-(2-(1-methylimidazol-4-yl)ethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| **33** | Int. A4<br>Int. F1 |  | N-(2-(1-methylimidazol-4-yl)ethyl)-2-[2-(4-fluorobenzyl)-5,6-trimethylene-4 oxo-4H-pyrimid-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |

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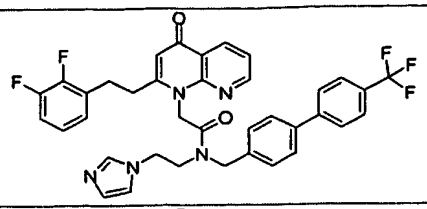
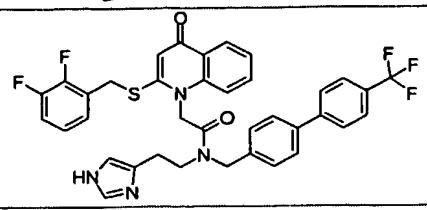
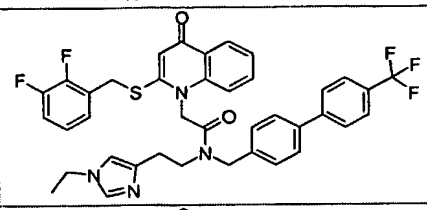
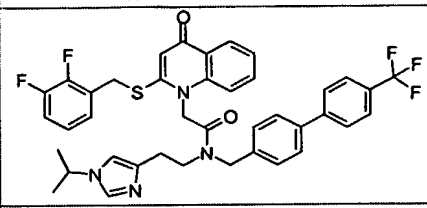
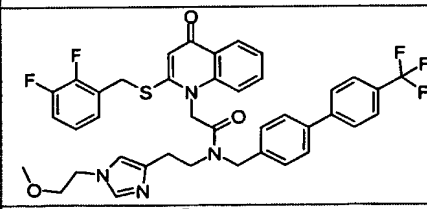
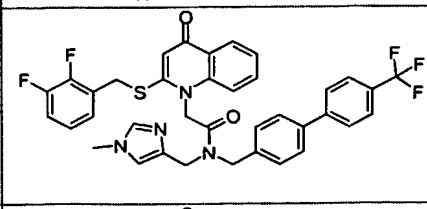
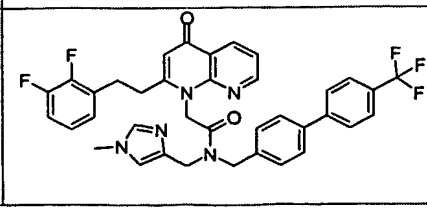
| **34** | Int. A56<br>Int. C6 |  | N-(2-(imidazol-1-yl)ethyl)-2-[2-(2-(2,3 difluorophenyl)ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |
| **35** | Int. A58<br>Int. D4 |  | N-(2-(imidazol-4-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin 1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| **36** | Int. A23<br>Int. D4 |  | N-(2-(1-ethylimidazol-4-yl)ethyl)-2-[2 (2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| **37** | Int. A24<br>Int. D4 |  | N-(2-(1-isopropylimidazol-4-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| **38** | Int. A50<br>Int. D4 |  | N-(2-(1-(2-methoxyethyl)imidazol-4-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoro methylbiphen-4-ylmethyl)acetamide |
| **39** | Int. A67<br>Int. D4 |  | N-((1-methylimidazol-4-yl)methyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| **40** | Int. A67<br>Int. C6 |  | N-((1-methylimidazol-4-yl)methyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |

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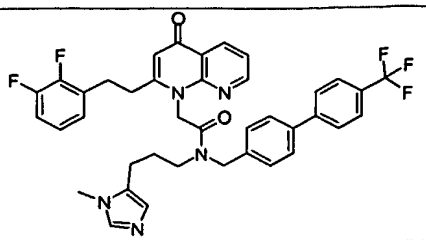
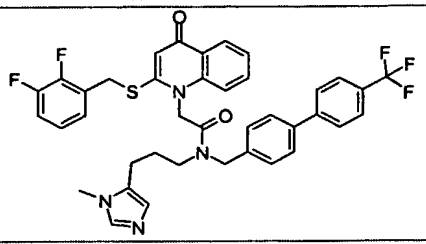
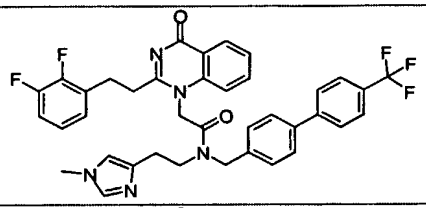
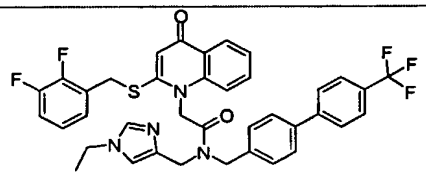
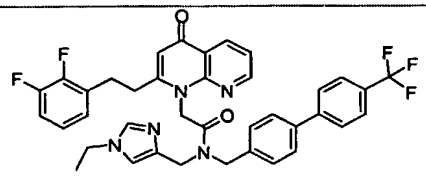
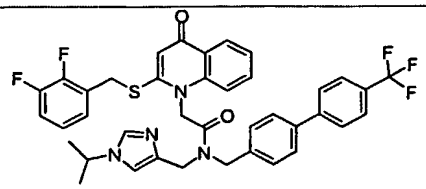
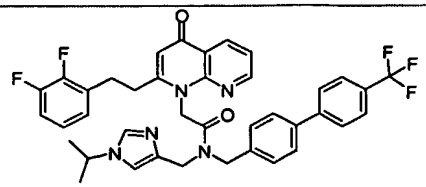
| 41 | Int. A66<br>Int. C6 |  | N-(3-(1-methylimidazol-5-yl)propyl)-2 [2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| 42 | Int. A66<br>Int. D4 |  | N-(3-(1-methylimidazol-5-yl)propyl)-2 [2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| 43 | Int. A4<br>Int. E3 |  | N-(2-(1-methylimidazol-4-yl)ethyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-quinazolin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |
| 44 | Int. A69<br>Int. D4 |  | N-((1-ethylimidazol-4-yl)methyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| 45 | Int. A69<br>Int. C6 |  | N-((1-ethylimidazol-4-yl)methyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H [1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |
| 46 | Int. A70<br>Int. D4 |  | N-((1-isopropylimidazol-4-yl)methyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H quinolin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| 47 | Int. A70<br>Int. C6 |  | N-((1-isopropylimidazol-4-yl)methyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |

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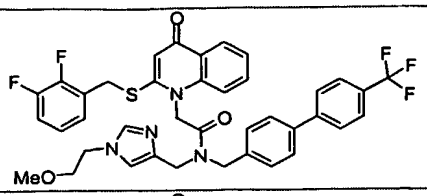
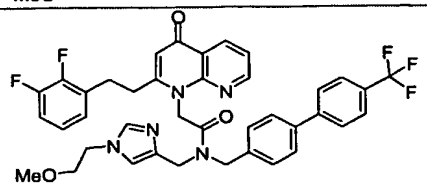
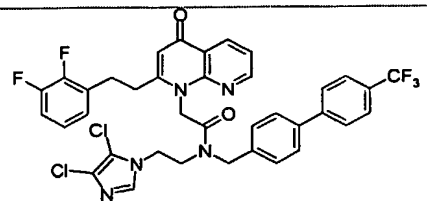
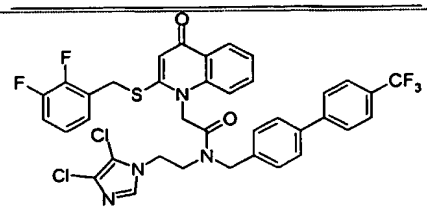
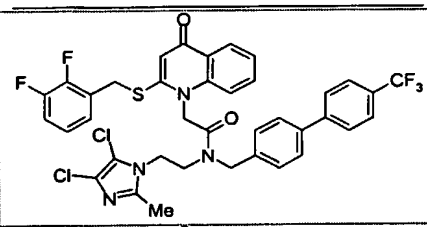
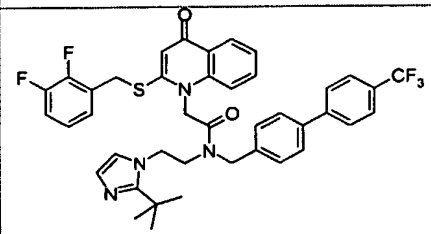
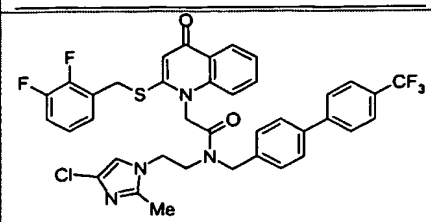
| 48 | Int. A71<br>Int. D4 |  | N-((1-(2-methoxyethyl)imidazol-4-yl)-methyl)-2-[2-(2,3-difluorobenzylthio)-4 oxo-4H-quinolin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |
| 49 | Int. A71<br>Int. C6 |  | N-((1-(2-methoxyethyl)imidazol-4-yl)-methyl)-2-[2-(2-(2,3-difluorophenyl)-ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)acetamide |
| | see Ex2 | | |
| 51 | Int A100<br>Int C6 |  | N-((1-(4,5-Dichloroimidazol-1-yl)-ethyl)-2-[2-(2-(2,3-difluorophenyl)-ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)acetamide |
| 52 | Int A100<br>Int D4 |  | N-(2-(4,5-Dichloroimidazol-1-yl)ethyl) 2-[2-(2,3-difluorobenzylthio)-4-oxo-4H quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| 53 | Int A101<br>Int D4 |  | N-(2-(4,5-Dichloro-2-methylimidazol-1 yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoro methylbiphen-4-ylmethyl)acetamide |
| 54 | Int A102<br>Int D4 |  | N-(2-(2-*t*-Butylimidazol-1-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| 55 | Int A103<br>Int D4 |  | N-(2-(4-Chloro-2-methylimidazol-1-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoro methylbiphen-4-ylmethyl)acetamide |

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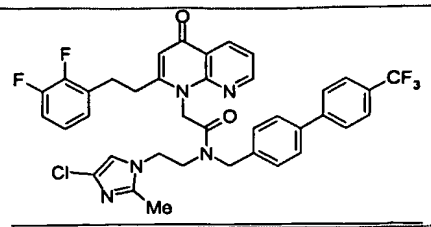
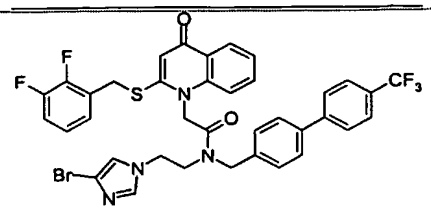
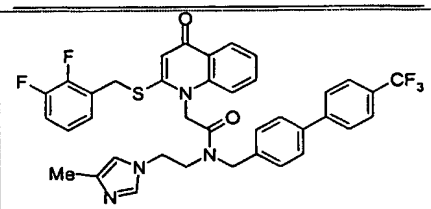
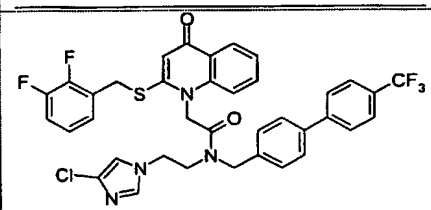
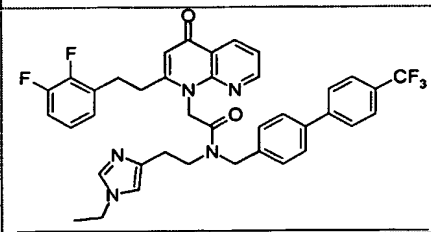
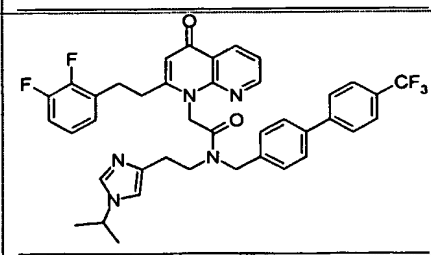
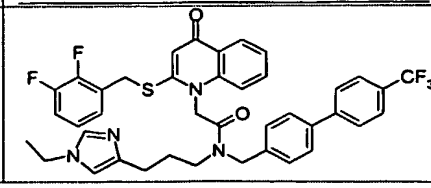
| **56** | Int A103<br>Int C6 |  | N-((1-(4-Chloro-2-methylimidazol-1-yl)ethyl)-2-[2-(2-(2,3-difluorophenyl)-ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)acetamide |
| **57** | Int A104<br>Int D4 |  | N-(2-(4-Bromoimidazol-1-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| **58** | Int A105<br>Int D4 |  | N-(2-(4-Methylimidazol-1-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| **59** | Int A106<br>Int D4 |  | N-(2-(4-Chloroimidazol-1-yl)ethyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| **60** | Int A23<br>Int C6 |  | N-(2-(1-Ethylimidazol-4-yl)ethyl)-2-[2(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H[1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |
| **61** | Int A24<br>Int C6 |  | N-(2-(1-*i*-Propylimidazol-4-yl)ethyl)-2[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-ylmethyl)-acetamide |
| **62** | Int A150<br>Int D4 |  | N-(3-(1-ethylimidazol-4-yl)propyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H-quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |

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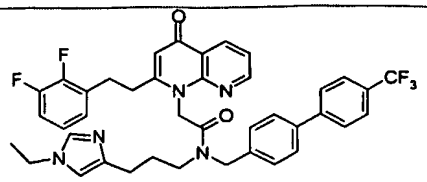
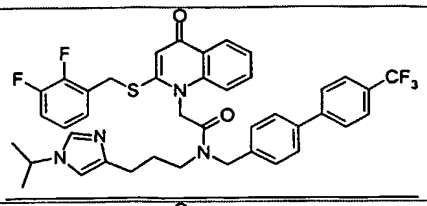
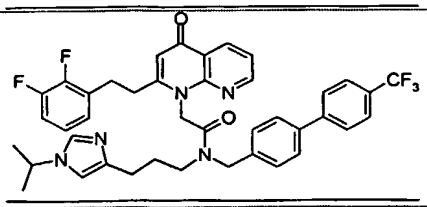
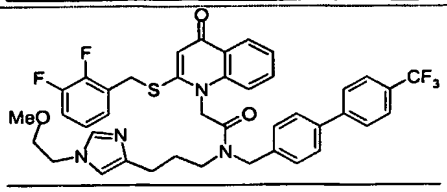
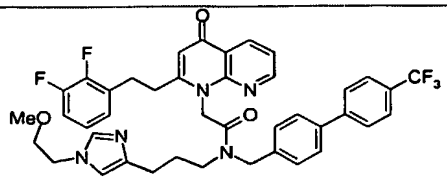
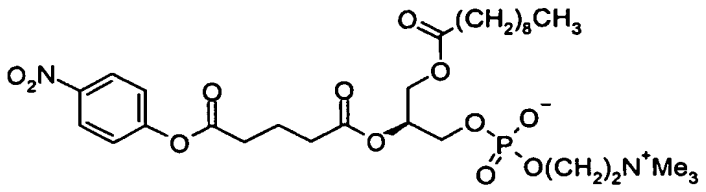
| 63 | Int A150<br>Int C6 |  | N-(3-(1-ethylimidazol-4-yl)propyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo 4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 64 | Int A151<br>Int D4 |  | N-(3-(1-*i*-propylimidazol-4-yl)propyl)-2-[2-(2,3-difluorobenzylthio)-4-oxo-4H quinolin-1-yl]-N-(4'-trifluoromethyl-biphen-4-ylmethyl)acetamide |
| 65 | Int A151<br>Int C6 |  | N-(3-(1-*i*-propylimidazol-4-yl)propyl)-2-[2-(2-(2,3-difluorophenyl)ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 66 | Int A152<br>Int D4 |  | N-(3-(1-(2-methoxyethyl)imidazol-4-yl)propyl)-2-[2-(2,3-difluoro-benzylthio)-4-oxo-4H-quinolin-1-yl]-N (4'-trifluoromethylbiphen-4-yl-methyl)acetamide |
| 67 | Int A152<br>Int C6 |  | N-(3-(1-(2-methoxyethyl)imidazol-4-yl)propyl)-2-[2-(2-(2,3-difluoro-phenyl)ethyl)-4-oxo-4H-[1,8]naphthyridin-1-yl]-N-(4'-trifluoro-methylbiphen-4-ylmethyl)acetamide |

**Biological Data**

**1. Screen for Lp-PLA$_2$ inhibition.**

Enzyme activity was determined by measuring the rate of turnover of the artificial substrate (A) at 37 C in 50mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid) buffer containing 150mM NaCl, pH 7.4.



(A)

Assays were performed in 96 well titre plates.
Recombinant LpPLA2 was purified to homogeneity from baculovirus infected Sf9 cells, using a zinc chelating column, blue sepharose affinity chromatography and an anion exchange column. Following purification and ultrafiltration, the enzyme was stored at 6mg/ml at 4°C. Assay plates of compound or vehicle plus buffer were set up using automated robotics to a volume of 170µl. The reaction was initiated by the addition of 20µl of 10x substrate (A) to give a final substrate concentration of 20µM and 10 µl of diluted enzyme to a final 0.1nM LpPLA2. The reaction was followed at 405 nm and 37 °C for 20 minutes using a plate reader with automatic mixing. The rate of reaction was measured as the rate of change of absorbance.

**Results**

The compounds described in the Examples were tested as described above and had $IC_{50}$ values in the range <0.1 to 100 nM.